MEDIATIONAL MODELS WITH MULTIPLE OUTCOMES IN CROSS-SECTIONAL AND LONGITUDINAL STUDIES

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Submitted to the Graduate Faculty of

Graduate School of Public Health in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2007

UNIVERSITY OF PITTSBURGH

Graduate School of Public Health

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Mediational analysis is used to explain how a predictor affects the outcome through an intervening variable called a mediator. In a cross-sectional study, the predictor, the mediator, and the outcome are measured at single time points and these time points need to be chronologically in the same order. In longitudinal mediational models, the outcome and the mediator are measured over the follow-up period also in the chronological order while the predictor is measured at a single time point.

The role of a mediator in cross-sectional mediational models with single outcomes is mostly assessed by two parametric tests, Sobel test and Clogg test. We have extended these tests to multiple outcomes. The extensions also include two bootstrap approaches. Simulation results show that in the presence of moderate correlation between the predictor and the mediator, the extended Clogg test has the most reliable Type I error rate and the highest power.

For longitudinal mediational models, we have discussed one scenario where the outcome process and the mediational process are described by linear growth curves. The total indirect effect of the predictor is defined as the effect of the predictor on the initial status and the growth rate of the outcome after accounting for the mediating effect of the initial status and the growth rate of the mediator. Inferential methods for the total indirect effect are proposed, using a formulation by random coefficient models. Results from a simulation study indicate the reliability of the proposed methods with large samples. An illustrative example using University of Pittsburgh Physical Activity Study (PittPAS) is given. The study seeks to investigate an important question about the differential effect of gender, if any, on the exercise behavior in young adulthood in relation to the exercise behavior in adolescence. Using the mediational model, we found the differential effect of gender on physical activity in young adulthood was mediated by the previous physical activities experience in adolescence.

The public health significance of the present work lies in the development of statistical procedures using cutting-edge methodologies to handle irregularly observed data, small samples and a finer characterization of the longitudinal outcome and mediational processes.

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PREFACE

I would first like to thank my mentor, Professor Sati Mazumdar. I feel extremely fortunate to spend my graduate study period under her continuous guidance and encouragement. I am deeply indebted to Drs. Mazumdar, Arena, Becker, and Schulz for their financial supports during my study in University of Pittsburgh. I would also like to thank Ms. Patricia R. Houck, and my Thesis Committee, Drs. Mazumdar, Arena, Rockette, Tang, and Thompson for their help and advice during my graduate education. I am grateful to the past and present members of the Department of Biostatistics, especially Drs. Youk and He who offered me great help with both knowledge and technical expertise. I thank my parents and my sister for their support and encouragement. Finally, my heartfelt gratitude goes to my wife, Jian Huang for her tremendous love and sacrifice over the past years.

1.0 INTRODUCTION

Mediational analysis is used to explain how a predictor affects the outcome through an intervening variable called a mediator. In a cross-sectional study, the predictor, the mediator, and the outcome are measured at single time point and the time points need to be chronologically in the same order. In longitudinal mediational models, the outcome and the mediator are measured over the follow-up period also in the chronological order while the predictor is measured at a single time point.

The role of a mediator in a cross-sectional mediational model is mostly assessed by Sobel test and Clogg test in a single outcome scenario (MacKinnon, Lockwood et al. 2002). This dissertation extended univariate cross-sectional mediational modeling approaches to mediational models with multiple outcomes. The extension lies in providing a formula for the hypothesis test of indirect effect for Clogg test. We have also extended Sobel test to multivariate outcomes. In addition, two bootstrap approaches are proposed based on Clogg's parametric approach. A Monte Carlo simulation study is performed to compare Type I error rates and statistical powers of the proposed approaches.

For the longitudinal mediational model (LMM), we formulated the indirect effect from a series of random coefficient models (RCMs). The random coefficient model is able to handle time-unstructured data, which is a common feature in many longitudinal studies. Next, we extended by latent growth curve modeling (LGCM) approach (Cheong, MacKinnon et al. 2003) to describe a mediational analysis in an LMM taking two components of a profile as mediators to explain two components of the profile of outcomes. We have also extended a test proposed by Bollen (1986), Sobel (1982), and Preacher and Hayes (2005) for testing the indirect effect and tested its accuracy by a simulation study. We provided an illustrative example elucidating these methods using data from the Pittsburgh Physical Activity Study (PittPAS) (Aaron DJ, Kriska AM et al. 1993), where 860 adolescents were followed from adolescence (Phase I) to young adulthood (Phase II) to examine the role of adolescents-physical activity (mediator) in the relationship between gender (predictor) and the physical activity in young adults (outcome).

1.1 PERTINENT LITERATURE REVIEW

Cross-sectional Mediational Models

Mediational analysis is used to explain how and why a predictor (*X*) affects the consequent outcome (*Y*) through one or more mediators (*Z*). The causal relation of *X* on *Y* through *Z* is defined as an *indirect effect* (Baron and Kenny 1986; Kraemer, Wilson et al. 2002).

When mediational models include only one *X*, one *Z*, and one *Y*, they are called simple mediational models (SMM) (Preacher, 2004). Univariate mediational models are defined when a univariate *Y* is involved in the models. Multiple mediational models involve multiple *Z* variables and multivariate mediational models involve multiple *Y* variables.

A schematic representation of a simple mediational model is shown in Figure 1. Panel A illustrates the *total effect* of the predictor *X* on the outcome *Y*. Panel B shows the *indirect effect* of *X* on *Y* through the mediator *Z* as well as the *direct effect* of *X* on *Y*. Equations 1.1 - 1.3 describe these models. The *total effect* is represented by β_1 which is the regression coefficient of the predictor on the outcome in equation 1.1 (Panel A). The *direct effect* is represented by β_2 , which is the regression coefficient of the predictor *X* on the outcome after controlling the effects of the mediator in equation 1.2 (Panel B). Parameters *a* and *b* are the regression coefficients in equations 1.2 and 1.3, respectively; ε , ν , and ξ are error terms. The *indirect effect* can be evaluated by $\beta_1 - \beta_2 = ab$ (MacKinnon, Warsi et al. 1995).

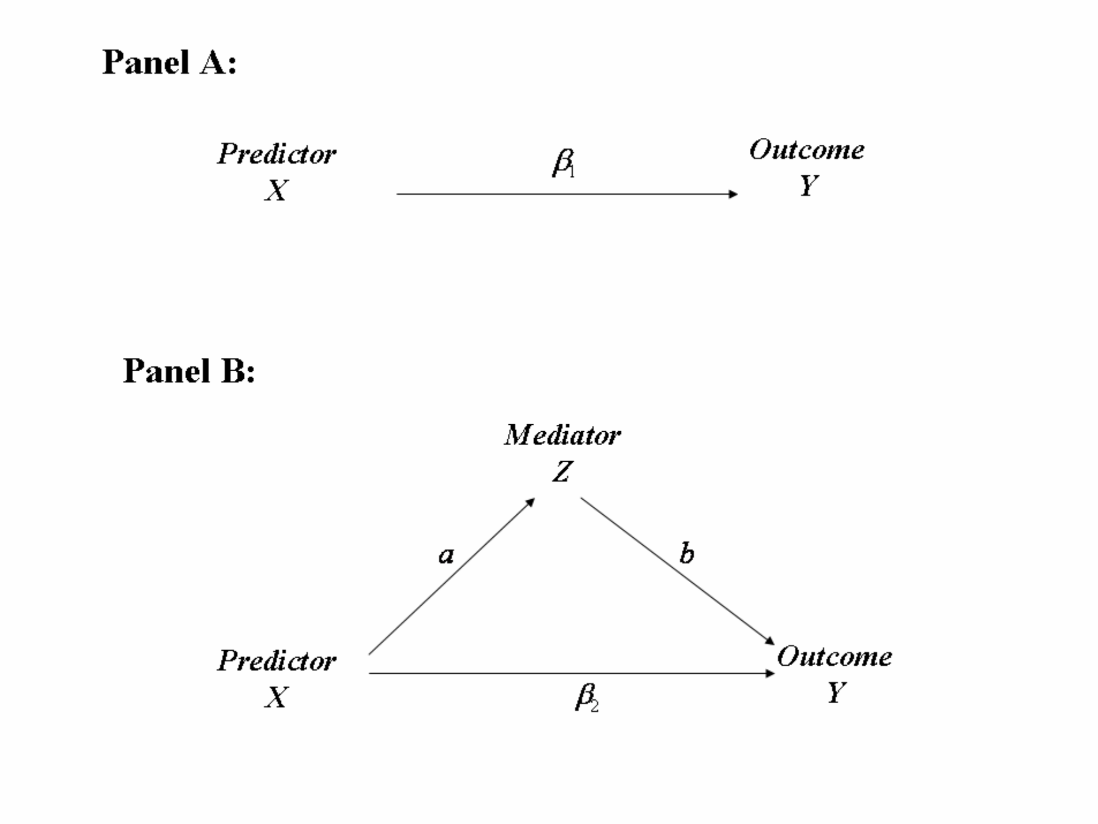


Fig 1. A schematic representation of a simple mediational model

$$Y = \beta_{00} + \beta_1 X + \varepsilon_{(1)} \tag{1.1}$$

$$Z = \beta_{01} + aX + \varepsilon_{(2)} \tag{1.2}$$

$$Y = \beta_{02} + \beta_2 X + bZ + \varepsilon_{(3)} \tag{1.3}$$

Several approaches have been proposed for estimating the *indirect effect* of the predictor on the outcome through the mediator. The most popular approach was proposed by Baron and Kenny (Baron and Kenny 1986). In their framework, the indirect effect exists when, 1) X significantly accounts for variability in Y; 2) X significantly accounts for variability in Z; 3) Z significantly accounts for variability in Y. If the mediator explains all of the observed effect of X on Y, the mediator is said to fully mediate the effect of X on Y. If the mediator explains a portion of the effects of X on Y, the mediator is said to partially mediate the effect of X on Y. Kraemer and her colleagues discussed mediation in randomized clinical trials (Kraemer, Stice et al. 2001; Kraemer, Wilson et al. 2002). Kraemer emphasized that a predictor should temporally precede the mediator. In clinical trials, this means that the mediator must be measured after the treatment randomization when X represents treatment. In Barron and Kenny's regression equations, only main effects of the predictor X and the mediator Z on the outcome Y (equation 1.2) are included. Here, Barron and Kenny's methodology is followed in order to maximize the generalizability.

In a simple mediational model, a statistical method for testing hypothesis about the indirect effect is to write the null hypothesis as H_0: $\beta_1 - \beta_2 = 0$. The corresponding statistical test is given by $t_{(n-3)} = (\hat{\beta}_1 - \hat{\beta}_2) / S_{\hat{\beta}_1 - \hat{\beta}_2}$ (Clogg and Shihadeh 1992) that is compared to the student-t critical values, where $S_{\hat{\beta}_1 - \hat{\beta}_2} = \left| \hat{\rho}_{XZ} S_{\hat{\beta}_2} \right|$ and $\hat{\rho}_{XZ}$ is the correlation between the predictor and the mediator and $S_{\hat{\beta}_2}$ is the standard error of $\hat{\beta}_2$.

Another approach for testing the existence of an indirect effect is to test $H_0 : ab = 0$. This hypothesis is usually tested by the Sobel test which compares the statistic $\hat{a}\hat{b} / S_{(\hat{a}\hat{b})}$ to the standard normal critical values (Sobel 1982). Sobel derived $S_{(\hat{a}\hat{b})}$ as $\sqrt{\hat{a}^2 S_{\hat{b}}^2 + \hat{b}^2 S_{\hat{a}}^2}$ from a Taylor expansion, where $\hat{a}$ and $\hat{b}$ are the least square estimates of a and b, $S_{\hat{a}}$ is the standard error of $\hat{a}$, and $S_{\hat{b}}$ is the standard error of $\hat{b}$.

MacKinnon and his colleagues compared fourteen methods of assessing the indirect effect (MacKinnon, Lockwood et al. 2002). It has been shown that Baron and Kenny's approach suffers from the lowest statistical power among the three methods. The Sobel test underestimates the Type I error rates (below 0.05) but provides a satisfactory power (greater than 0.80) to detect small, medium, and large effects until the sample size reaches 1000, 100, and 50 respectively. The Clogg test has accurate Type I error rates in most cases and the power was higher than the Sobel test.

One of the assumptions in these two parametric approaches (the Sobel test and the Clogg test) is the requirement of a large sample size, so that the point estimates of the indirect effect can be assumed to follow a normal distribution. This assumption often does not hold. An alternative approach for testing the indirect effect is the bootstrap method. By repeatedly sampling with replacement from the real data, many bootstrap samples are created and the test statistic is derived from each sample. The subsequent statistical inference is based on the sampling distributions of the test statistics (Bollen and Stine 1990; Efron and Tibshirani 1993; Shrout and Bolger 2002; Preacher and Hayes 2004).

There is an increasing interest in mediational analysis in various research areas (MacKinnon, Lockwood et al. 2002; Preacher and Hayes 2004). However, not much attention is given to mediational analysis with multiple outcomes. In a study examining the role of processing speed and spontaneous tempo slowing (mediators) in the relationship of age (predictor) and working memory (outcome), three measures of working memory were transformed into one principal component (Baudouin, Vanneste et al. 2004). In a study examining the role of religiosity in the relationship between stress and well-being in caregivers of spouses with Alzheimer’s disease (Leblanc, Driscoll et al. 2004), depression and overall physical health in caregivers were measured as two outcomes representing well-being. Caregivers were separated into two groups, better or worse, according to their physical health situation. Univariate mediational analysis was then applied in each group for stress (predictor), religiosity (mediator), and depression. It would be more informative to find out if religiosity plays any role in the relationship between stress and overall well-being. Studies mostly use several separate univariate models instead of one single multivariate mediational model. Rosen and his colleagues (Rosen, Seidman et al. 2004) examined the role of mood (mediator) between erectile dysfunction (predictor) and two outcomes, the sexual quality life and family life using two separate simple mediational models. However, the sexual quality life and family life were significantly correlated to each other and the Type I error may be a concern. The advantages of multivariate mediational models are:

a) Easy interpretability: One model with multiple correlated outcomes could determine whether the *total indirect effect* of X to a set of Ys through Z exists.

b) Control of Type I error: Multivariate responses are usually correlated. The Type I error rate could be inflated if multivariate mediation hypotheses are tested with multiple hypotheses with one outcome at a time (Goodwin 1984).

c) Inclusion of several outcomes in one model allows the examination of differential effects of Z on the outcomes.

Longitudinal Mediational Models

Longitudinal data structures are common in different areas of social science and epidemiological studies. The longitudinal mediational model (LMM) is defined as having the mediator and outcome measured over the follow-up period. Investigation of the indirect effect in an LMM could be attained by latent growth curve modeling (LGCM) (Cheong, MacKinnon et al. 2003). Cheong's model focused on prevention trials and the indirect effect is defined as the change in the outcome influenced by the changes in the mediator, which is influenced by the predictor. The indirect effect was tested by the Sobel test.

The basic LGCM can be viewed as a common factor model (MacCallum, Kim et al. 1997; Cheong, MacKinnon et al. 2003):

$$Y_i = \Lambda \eta_i + e_i \tag{1.4}$$

where vector Y_i represents the repeated outcomes of the individual i over T time points, ($t=1,2\ldots T$). In this equation, Λ is a factor loading matrix of order T by J. The columns of Λ are called basis functions, which represent specific aspects of the change in Y (Meredith and Tisak 1990), η_i is a J by 1 vector of J latent constructs, and e_i is a vector of residuals. Equation 1.4 is called the Level I model for each individual. We usually assume a multivariate normal distribution for the residuals. If we further assume that the outcome variable is a linear function of time, the two factor model from 1.4 provides

$$Y_i = \begin{bmatrix} Y_{i1} \\ Y_{i2} \\ . \\ Y_{iT} \end{bmatrix}, \quad \Lambda = \begin{bmatrix} 1 & x_1 \\ 1 & x_2 \\ . & . \\ 1 & x_T \end{bmatrix}, \quad \eta_i = \begin{bmatrix} \eta_{\text{int\_}i} \\ \eta_{\text{slope\_}i} \end{bmatrix} \text{ and } e_i = \begin{bmatrix} e_{i1} \\ e_{i2} \\ . \\ e_{iT} \end{bmatrix} \tag{1.5}$$

where ($x_1, x_2, ... x_T$) represents the measure of time for individual *i*, η_{int_i} is the intercept parameter describing the subject's initial score (model-based) at baseline, η_{slope_i} is the slope parameter describing the subject's rate of change in the outcome over time, and $(e_{i1}, e_{i2}, ... e_{iT})$ represents the residual vector.

The Level II model aims to investigate whether inter-individual heterogeneity in the latent constructs can be predicted by other variables. Referring to equation 1.5, the Level II model, $\eta_i = \pi + \gamma\xi_i + D_i$, can be specified as:

$$\begin{bmatrix} \eta_{\text{int}\_i} \\ \eta_{\text{slope}\_i} \end{bmatrix} = \begin{bmatrix} \pi_0 \\ \pi_1 \end{bmatrix} + \begin{bmatrix} \gamma_{11} & \gamma_{12} \\ \gamma_{21} & \gamma_{22} \end{bmatrix} \begin{bmatrix} \xi_{1i} \\ \xi_{2i} \end{bmatrix} + \begin{bmatrix} D_{0i} \\ D_{1i} \end{bmatrix} \tag{1.6}$$

where the individual's initial values and the slopes are modeled as linear functions of the predictors. The vector π provides the intercept terms, γ is the loading matrix, vector ξ represents the values of the predictors and *D* is the residual vector. In this model, we usually assume that the residual vector *D* is distributed as a multivariate normal with zero means vector and a specified covariance matrix.

A typical LGCM is represented by time-structured data, usually evenly spaced for all individuals. However, the formulation of LGCM by random coefficient models (RCMs) does not require this assumption and accommodates time-unstructured data by treating time as an observation variable (MacCallum, Kim et al. 1997).

2.0 METHOD

2.1 MULTIVARIATE MEDIATIONAL MODELS OF ONE MEDIATOR AND MULTIPLE OUTCOMES

Figure 1 and equations 1.1 – 1.3 can be extended to multiple outcomes, with *Y* representing a continuous *k*-variate outcome, *X* and *Z* remaining the same as before (Figure 2). In equations 1.1 and 1.2, *Y* is replaced by an *n* by *k* matrix with *n* independent subjects; β_1 and β_2 are vectors of size *k* and represent the regression coefficients of *X* on *Y* with or without adjusting the effect of *Z*; *b* is replaced by a vector of size *k* while *a* is not changed (scalar). We assume the basic multivariate regression assumptions, which include multivariate normality of the residuals, homoscedasticity of the residual variance, and a common covariance structure across observations.

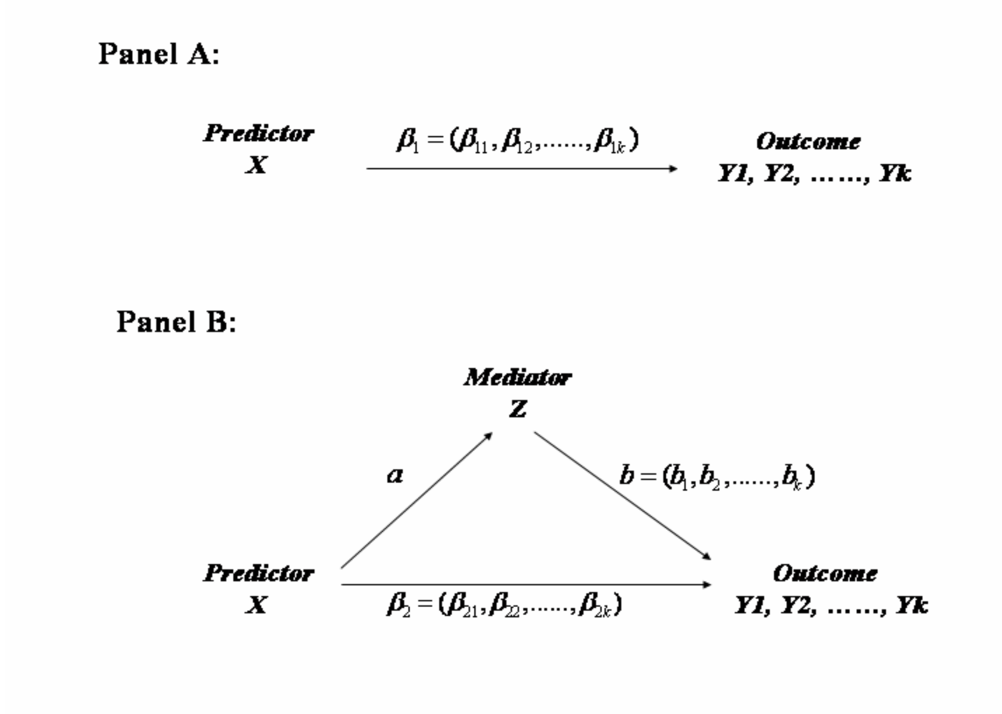


Fig 2. A schematic representation of a multivariate mediational model

2.1.1 Extended Methods

Extended Clogg Parametric Test (ECLG-P)

The *total indirect effect* of the predictor to all the outcomes through the mediator can be described as $\delta = \beta_1 - \beta_2$. By writing δ as $(\delta_1, \delta_2, ..., \delta_k)$, the null hypothesis can be represented by k individual hypothesis to be tested simultaneously, and $\delta_j = \beta_{1j} - \beta_{2j}$ represents the specific indirect effect of the predictor to the jth outcome through the mediator, $j = 1, 2......, k$.

The least square estimators of β_1, β_2 and b in equations 1.1 and 1.2 are

$$\hat{\beta}_1 = (X'X)^{-1}X'Y \tag{2.1}$$

$$\hat{\beta}_2 = (X'X)^{-1}X'(Y - Z\hat{b}) \tag{2.2}$$

$$\hat{b} = (Z'Z)^{-}Z'Y \tag{2.3}$$

Let $\hat{\delta} = \hat{\beta}_1 - \hat{\beta}_2 = WY$ where $W = (X'X)^{-1}X'Z(Z'Z)^{-1}Z'$.

The variance-covariance matrix of $\hat{\delta} = \hat{\beta}_1 - \hat{\beta}_2 = WY$, $V(\hat{\delta})$, can be estimated by calculating the quantities $V(\hat{\delta}_{ij}) = W\hat{\sigma}_{ij}W'$ where $\hat{\sigma}_v = (\hat{\sigma}_{ij})$. Let r be the total number of predictors and mediators. $\hat{\sigma}_v$ is estimated by $\hat{v}'\hat{v}/(n-r)$ where $\hat{v} = Y - X\hat{\beta}_2 - Z\hat{b}$. The statistic $T_1 = \hat{\delta}[V(\hat{\delta})]^{-1}\hat{\delta}'$ could be used to test the total indirect effect of the predictor on all the outcomes through the mediator. The $[(n-k-r+1)/k(n-r)]T_1$ follows an F distribution with degrees of freedom k and n-k-r+1. The null hypothesis is rejected if

$[(n-k-r+1)/k(n-r)]T_1$ is larger than $F_{k,n-k-r+1,(\alpha)}$. In the present situation, we have one predictor (*X*) and one mediator (*Z*). Hence, *r* = 2.

Extended Sobel Parametric Method (ESOB-P)

We extended the Sobel parametric test and called it ESOB-P. Point estimates and the corresponding standard error of the total indirect effect are obtained from Bollen's matrix formulae (Bollen 1987). The multivariate point estimate is a vector of size *k*, given by $\hat{\Lambda} = (\hat{a}\hat{b}_1,\ \hat{a}\hat{b}_2,\ \ldots..,\ \hat{a}\hat{b}_k)$. Derived by multivariate Delta method, the covariance matrix for the total indirect effect estimate is given by:

$$V(\hat{\Lambda}) = \begin{bmatrix} \hat{b}_1^2\hat{\sigma}_a^2 + \hat{a}^2\hat{\sigma}_{\hat{b}_1}^2 & \hat{b}_1\hat{b}_2\hat{\sigma}_a^2 + \hat{a}^2\hat{\sigma}_{\hat{b}_1\hat{b}_2} & . & . & . & \hat{b}_1\hat{b}_k\hat{\sigma}_a^2 + \hat{a}^2\hat{\sigma}_{\hat{b}_1\hat{b}_k} \\ \hat{b}_1\hat{b}_2\hat{\sigma}_a^2 + \hat{a}^2\hat{\sigma}_{\hat{b}_1\hat{b}_2} & \hat{b}_2^2\hat{\sigma}_a^2 + \hat{a}^2\hat{\sigma}_{\hat{b}_2}^2 & & & & . \\ . & . & . & & & . \\ . & . & & . & & . \\ . & . & & & . & . \\ \hat{b}_1\hat{b}_k\hat{\sigma}_a^2 + \hat{a}^2\hat{\sigma}_{\hat{b}_1\hat{b}_k} & . & . & . & . & \hat{b}_k^2\hat{\sigma}_a^2 + \hat{a}^2\hat{\sigma}_{\hat{b}_k}^2 \end{bmatrix}$$

where $\hat{a}$ and $\hat{\sigma}_{\hat{a}}^2$ are estimated by fitting the model (1.3), $\hat{b}$ is given by the equation 2.3 and $Cov(\hat{b}) = Cov[(Z'Z)^{-}Z'Y] = (Z'Z)^{-}\hat{\sigma}_v$; *Z*, *Q*, and $\hat{\sigma}_v$ are defined in the earlier section. The test statistic $T_2 = \hat{\Lambda}[V(\hat{\Lambda})]^{-1}\hat{\Lambda}'$, which follows χ_k^2, could be used to test the total indirect effect. We should note here that distributional assumption of Sobel test and the extended Sobel test are justified under the large sample approximation (MacKinnon, Lockwood et al. 2004; Preacher and Hayes 2004).

Bootstrap Method I (BS-I)

Let θ be the parameter of interest and $\Sigma = \mathrm{var}(\theta)$. For the ECLG-P, $\theta = \beta_1 - \beta_2$. We term the Bootstrap method I, which is based on the parameters estimated using the ECLG-P, as BS-I.

The Bootstrap method I consists of the following steps:

1) Calculate the $\hat{\theta}$, $\hat{\Sigma}$ and $\hat{T} = \hat{\theta}\hat{\Sigma}^{-1}\hat{\theta}'$ from observed data using ECLG-P.

2) Repeatedly sample with replacement from the observed data to generate *B* bootstrap samples. Let $\hat{\theta}_i^*$ and $\hat{\Sigma}_i^*$ denote the bootstrap versions of $\hat{\theta}$ and $\hat{\Sigma}$, calculated from the *i*th bootstrap sample, $i, = 1,2.....B$. Then calculate $\hat{T}_i^* = (\hat{\theta} - \hat{\theta}_i^*)\hat{\Sigma}_i^{*-1}(\hat{\theta}' - \hat{\theta}_i^{*}{}')$.

3) Use the $\frac{\alpha}{2}$ th and $(1-\frac{\alpha}{2})$ th percentiles of the bootstrap distribution of $\hat{T}^*$ to obtain the "bootstrap critical interval" ($\hat{T}^*_{\frac{\alpha}{2}}$, $\hat{T}^*_{1-\frac{\alpha}{2}}$).

4) The rejection of the null hypothesis is failed if $\hat{T}$ falls into the interval ($\hat{T}^*_{\frac{\alpha}{2}}$, $\hat{T}^*_{1-\frac{\alpha}{2}}$).

Bootstrap Method II (BS-II)

We propose another bootstrap method to test the indirect effect and term it BS-II. Let $\hat{\delta}_b = \hat{\beta}_{1b} - \hat{\beta}_{2b}$ in each bootstrap sample. The bootstrap mean is $\hat{\delta}^* = \frac{1}{B}\sum_{b=1}^{B}\hat{\delta}_b$. The standard error of the $\hat{\delta}^*$ is $V(\hat{\delta}^*) = \frac{1}{B-1}(\hat{\delta}_b - \hat{\delta}^*) \times (\hat{\delta}_b - \hat{\delta}^*)'$

We assume that $\hat{\delta}$ follows a multivariate normal distribution. The test statistic for the overall indirect effect is $T_3 = \hat{\delta}^* \times [V(\hat{\delta}^*)]^{-1} \times \hat{\delta}^*{}'$ with $T_3[(B-k)/k(B-1)]$ following an *F* distribution with degrees of freedom *k* and *B-k*. Therefore, the null hypothesis is rejected approximately if T_3 is larger than $\frac{(B-1)k}{B-k}F_{k,B-k,(\alpha)}$.

2.1.2 Monte Carlo Study for the Comparison of the Extended Methods

Study Design

The purpose of this Monte Carlo study is to investigate Type I error rates and power rates for the four methods: ECLG-P, ESOB-P, BS-I, and BS-II.

For the parametric methods, sample sizes are chosen as 25, 50, 100, 200, 500, and 1000. For the bootstrap methods, sample sizes are chosen as 25, 50, 100, 200, and 500. The number of outcomes is taken as three. The three outcome variables are simulated from a multivariate normal distribution with no correlation (0), small (0.3), and high (0.6). β_1 is set to (0.2, 0.2, 0.2). We varied values of the indirect effect by changing *a* and *b* where *b* are set as (0, 0, 0), (0.2, 0.2, 0.2), (0.4, 0.4, 0.4), or (0.55, 0.55, 0.55), and a is chosen to be 0, 0.2 and 0.5.

For each condition, 500 data sets were created in the SAS (Version 9.13) programming language using methods based on the work of previous studies (MacKinnon, Warsi et al. 1995; MacKinnon, Lockwood et al. 2002; Cheong, MacKinnon et al. 2003). The proportion of replications rejecting the null hypothesis of no indirect effect provided an estimate of the Type I error rate and statistical power. We use the 5% (of 500 replications) significant level. The indirect effects are expected to be statistically significant in 25 of the 500 samples when *ab* equals zero. The situations of no indirect effect are either $a = 0$, or $b = 0$, or both $a = 0$ and $b = 0$. When *ab* is not equals zero, the percentages provided the measure of statistical power.

Simulation Results

Table 1 to 6 present percentages of the Type I error rates and the empirical power rates for different magnitudes of the correlation between the outcomes. The tables were organized to represent the rejection rates under different combinations of *a* and *b*.

Evaluation of the Type I error rate was performed for three conditions: both *a* and *b* were zero, *a* alone was zero, and *b* alone was zero. ECLG-P overestimated (much greater than 5%) Type I error rates when *b* alone was nonzero. In practical studies, *a* could hardly be zero because one of the requirements for a mediator is that the correlation between the predictor and the mediator exists. In other situations, the Type I error rates were around nominal value. ESOB-P showed lower Type I error rates than 5% in all combinations excepting in large sample size (500 and 1000) groups. In these groups, ESOB-P's type I error rate was around 5%.

ECLG-P showed the greatest power. The power decreased when *a* increased alone. When there was no correlation between the outcomes (Table 4), ECLG-P achieved satisfactory power (greater than 0.8) in most situations. Powers were lower than 0.8 only in the situations where *b* was small and sample size was smaller than 100. The power decreased when the correlations between the outcomes increased. Under the same situations, ECLG-P needed 200 subjects to reach satisfactory power when high correlations (0.6) presented (Table 6). When the elements in *b* were larger than 0.2, ECLG-P was able to detect significant indirect effects with a sample size of 50.

The powers of ESOB-P increased with both *a* and *b*. The power values were more sensitive to values of *a* than those of *b*. In Table 4, in the presence of high correlation between the predictor and the mediator (0.5), ESOB-P had satisfactory power to detect significant indirect effects at sample sizes of 200, 100, and 50, corresponding to small, moderate, and large *b* values.

In Table 6, the required sample size rose to 500, 100, and, 100. The ESOB-P had unsatisfactory power when the correlation between the predictor and the mediator was low (0.2). Similar to ECLG-P, the powers decreased as the outcomes correlation increased. For a large sample size (500), ESOB-P showed satisfactory power in all situations.

BS-I had similar performance as ECLG-P in Type I error rates except in the situation where *b* alone was nonzero. This method had the lowest power in all of these four methods. When *a* was small, the method was unable to reach satisfactory power even in sample size of 500.

Compared to ESOB-P, BS-II had slightly higher Type I error rates and power. It had all of the large sample properties of ESOB-P with small sample sizes. When *a* was small (0.2), this method had unsatisfactory power, especially when correlations existed in the outcomes. Similar to ESOB-P, BS-II was able to detect significant indirect effects in all situations with a sample size of 500.

Table 1. Type I error rates in % ; correlations between outcomes are set at 0.

Parameter	Method	Sample size (*n*)					
		25	50	100	200	500	1000
a=0*	ECLG-P	4.4	4	3.8	5	4.6	4.4
b=(0, 0, 0)	ESOB-P	0	0	0	0	0	0
	BS-I	2.2	2.8	3.6	2.8	3.6	
	BS-II	0	0	0	0	0	
a=0.2	ECLG-P	5.6	4	5.6	4.6	4.2	5.6
b=(0, 0, 0)	ESOB-P	0	0	0	0	0.6	3
	BS-I	3	2.8	3.4	3.6	3.4	
	BS-II	0.2	0	0	0	0.8	
a=0.5	ECLG-P	4	58	4.2	4.2	5.6	4.6
b=(0, 0, 0)	ESOB-P	1.6	1.4	2.0	2.4	5.2	4.2
	BS-I	2.2	2.4	4.4	2.8	5.2	
	BS-II	3.2	2.8	1.6	2.8	3.6	
a=0*	ECLG-P	97.4	100	100	100	100	100
b=(.4, .4, .4)	ESOB-P	0	0.2	0.8	0.4	0.2	0.4
	BS-I	0	0	0	0	0	
	BS-II	1.4	0.6	1.4	0.2	0.4	

Table 2. Type I error rates in % ; correlations between outcomes are set at 0.3.

Parameter	Method	Sample size (*n*)					
		25	50	100	200	500	1000
a=0*	ECLG-P	4.4	4.6	4.8	4.2	4	4.4
b=(0, 0, 0)	ESOB-P	0	0	0	0	0	0
	BS-I	1.6	1.4	2.6	4.2	3.8	
	BS-II	0	0	0	0	0	
a=0.2	ECLG-P	4.6	5	4.6	4.4	5	5.2
b=(0, 0, 0)	ESOB-P	0	0.2	0	0	0.4	2.2
	BS-I	2.6	3.4	2.8	2.8	4.4	
	BS-II	0	0	0	0	0.8	
a=0.5	ECLG-P	4.6	4	4.8	4.2	5	5.2
b=(0, 0, 0)	ESOB-P	0.8	0.8	2.2	4	4.2	4.8
	BS-I	1.6	2.4	3.6	5.4	5.8	
	BS-II	2.2	2.2	3.2	5	3.6	
a=0*	ECLG-P	71.8	97	100	100	100	100
b=(.4, .4, .4)	ESOB-P	0.2	0	0.4	0.4	0.4	0.2
	BS-I	0.2	0	0	0	0	
	BS-II	0.2	0.2	0.4	0.6	0.4	

Table 3. Type I error rates in % ; correlations between outcomes are set at 0.6.

Parameter	Method	Sample size (*n*)					
		25	50	100	200	500	1000
a=0*	ECLG-P	3.2	4.4	4.6	5	4	4.8
b=(0, 0, 0)	ESOB-P	0	0	0	0	0	0
	BS-I	3.4	2.8	4.6	2.2	2.6	
	BS-II	0	0	0	0	0	
a=0.2	ECLG-P	5	4.2	3.6	6.2	4.6	4.8
b=(0, 0, 0)	ESOB-P	0	0	0	0	0.8	2.4
	BS-I	3	2.6	2	2.4	2.4	
	BS-II	0	0	0	0	0	
a=0.5	ECLG-P	4.4	4	5.2	4.6	4.2	5.2
b=(0, 0, 0)	ESOB-P	0.2	0.6	3.8	3.4	3.4	5
	BS-I	4.4	1.6	2.6	5.4	3.6	
	BS-II	1.8	1.4	4.2	4.2	4.6	
a=0*	ECLG-P	53.6	87.6	99	100	100	100
b=(.4, .4, .4)	ESOB-P	0	0	0	0.2	0.2	0.8
	BS-I	0.6	0	0	0	0	
	BS-II	0.2	0	0.2	0.2	0.4	

ECLG-P: Extended Clogg parametric method;
ESOB-P: Extended Sobel parametric method;
BS-I: Bootstrap method I ; BS-II: Bootstrap method II
* The situations when *a*=0 are not plausible in practical studies.

Table 4. Simulated power values in % ; correlations between outcomes are set at 0

Parameter	Method	Sample size (*n*)					
		25	50	100	200	500	1000
a=0.2	ECLG-P	29.4	56.8	89	100	100	100
b=(.2, .2, .2)	ESOB-P	0.2	0.4	5	32	93.8	100
	BS-I	0.8	0.6	1.2	10.8	73	
	BS-II	1	1.6	7	32.2	95.6	
a=0.5	ECLG-P	21.6	46	80.4	98	100	100
b=(.2, .2, .2)	ESOB-P	2.6	16.6	67	97	100	100
	BS-I	1	8	54.2	95.2	100	
	BS-II	6.2	22.2	67.4	96.2	100	
a=0.2	ECLG-P	96.4	100	100	100	100	100
b=(.4, .4, .4)	ESOB-P	0	5.8	20.4	55.2	96.4	99.8
	BS-I	0.2	1.4	4.6	17.8	74.0	
	BS-II	3.2	7.2	22.8	56.8	96.2	
a=0.5	ECLG-P	82.6	99.6	100	100	100	100
b=(.4, .4, .4)	ESOB-P	24.4	76.2	99.4	100	100	100
	BS-I	5.8	42.2	91.6	100	100	
	BS-II	33.6	76	99.4	100	100	
a =0.2	ECLG-P	100	100	100	100	100	100
b=(.55, .55, .55)	ESOB-P	5.2	8.2	22.8	52.8	95.4	100
	BS-I	1.6	2.6	4.6	17.4	72.4	
	BS-II	7.2	11	26	53	96.6	
a =0.5	ECLG-P	100	100	100	100	100	100
b=(.55, .55 .55)	ESOB-P	53	87.2	100	100	100	100
	BS-I	18.6	54.8	93.4	100	100	
	BS-II	55.4	88	100	100	100	

ECLG-P: Extended Clogg parametric method;
ESOB-P: Extended Sobel parametric method;
BS-I: Bootstrap method I ; BS-II: Bootstrap method II

Table 5. Simulated power values in % ; correlations between outcomes are set at 0.3

Parameter	Method	Sample size (*n*)					
		25	50	100	200	500	1000
a=0.2	ECLG-P	16.2	33	71.2	93	100	100
b=(.2, .2, .2)	ESOB-P	0.2	0.2	1	20.6	91.2	100
	BS-I	1.2	0.8	0.4	5	68	
	BS-II	0.6	1	1.8	21.2	90.6	
a=0.5	ECLG-P	15.2	28.2	56.6	87.4	100	100
b=(.2, .2, .2)	ESOB-P	1.4	6.2	34.2	83.6	100	100
	BS-I	0.4	2.4	23.4	75.6	99.6	
	BS-II	4	11.4	37.8	83.2	99.8	
a=0.2	ECLG-P	70	96.4	100	100	100	100
b=(.4, .4, .4)	ESOB-P	0.6	3.6	16	46.2	96.2	100
	BS-I	0.4	0.6	4.8	14	74.8	
	BS-II	1.8	6.2	16.6	47.2	94.4	
a=0.5	ECLG-P	52.2	90	99.6	100	100	100
b=(.4, .4, .4)	ESOB-P	8.8	55.4	99.2	100	100	100
	BS-I	2.4	27	91.8	100	100	
	BS-II	16	56.8	97.6	100	100	
a =0.2	ECLG-P	99.2	100	100	100	100	100
b=(.55, .55, .55)	ESOB-P	3.2	7.6	19.4	50.2	96.2	100
	BS-I	0.4	1.4	4.2	17.6	74.2	
	BS-II	5.4	8.6	21	58	95.4	
a =0.5	ECLG-P	100	100	100	100	100	100
b=(.55, .55 .55)	ESOB-P	36.4	83.8	99.4	100	100	100
	BS-I	10.2	51.2	92.6	100	100	
	BS-II	40.6	84.4	99.2	100	100	

ECLG-P: Extended Clogg parametric method;
ESOB-P: Extended Sobel parametric method;
BS-I: Bootstrap method I ; BS-II: Bootstrap method II

Table 6. Simulated power values in % ; correlations between outcomes are set at 0.6

Parameter	Method	Sample size (*n*)					
		25	50	100	200	500	1000
a=0.2	ECLG-P	15.4	26.4	52	78.2	100	100
b=(.2, .2, .2)	ESOB-P	0	0	1.6	12.8	86.8	100
	BS-I	0.2	0.4	0.6	5.4	67.2	
	BS-II	0.4	0.4	1.8	13.2	90.2	
a=0.5	ECLG-P	11.4	21.4	38.8	72.4	98.4	100
b=(.2, .2, .2)	ESOB-P	1.4	6.2	23	65	98.6	100
	BS-I	1.2	3.6	15.6	57.6	97.4	
	BS-II	3.6	8.8	26	64.8	98.4	
a=0.2	ECLG-P	49.4	85.2	99.6	100	100	100
b=(.4, .4, .4)	ESOB-P	0.2	1.6	10.2	44.8	94	100
	BS-I	0	0.4	2.8	13.6	73.6	
	BS-II	2	4.2	11.6	46.8	95.6	
a=0.5	ECLG-P	38.6	76.6	97.8	100	100	100
b=(.4, .4, .4)	ESOB-P	5.2	36	91.6	100	100	100
	BS-I	1.4	16.4	79.2	100	100	
	BS-II	12.6	39.4	90.2	100	100	
a=0.2	ECLG-P	85.2	99	100	100	100	100
b=(.55, .55, .55)	ESOB-P	1.2	4.8	21.4	46.2	96	100
	BS-I	0.6	1.4	6	12	73.2	
	BS-II	3.6	6.6	22.8	48.8	94.2	
a=0.5	ECLG-P	73.4	96.6	100	100	100	100
b=(.55, .55 .55)	ESOB-P	22.8	76.2	99.2	100	100	100
	BS-I	6	47.6	88.6	100	100	
	BS-II	27.6	77.2	98.6	100	100	

ECLG-P: Extended Clogg parametric method;
ESOB-P: Extended Sobel parametric method;
BS-I: Bootstrap method I ; BS-II: Bootstrap method II

2.1.3 Statistical Issue

The indirect effect in mediational model depends on the extent to which the predictor affects the mediator (*a*) and the extent to which the mediator affects the outcome considering the mediator (*b*). In the Monte Carlo Study when $a = 0$, or $b = 0$, or both $a = 0$ and $b = 0$, the proportion of replications in which the null hypothesis of no indirect effect was rejected provided an estimate of the Type I error rate. The situation when $a = 0$ is interpreted as no correlation between the predictor and the mediator, which is not plausible in practical mediational studies. The correlation between the predictor and mediator is one of the key requirements for a mediator. Without this correlation, the causal relationship will be failed to build in the first step before performing hypothesis test of the indirect effect (Baron and Kenny 1986; Kraemer, Wilson et al. 2002). Therefore, mediational models are not supposed to be used when $a = 0$. The parameter b represents the relation between the mediator and the outcome accounting for the effect of the predictor. When $b = 0$, this relation is zero, and there is no indirect effect. The Type I error rates for $b = 0$ is not a concern in our study. When both *a* and *b* do not equal zero, the indirect effect is said to exist. The proportion of times that each method led to the conclusion that the indirect effect was significant provided the measure of statistical power.

Overall, the result of ECLG-P and ESOB-P in multivariate mediational model is consistent with the result in SMM. When there is no correlation between the outcomes, the Type I error rates and powers in Table 1 and Table 4 are similar to MacKinnon's result (MacKinnon, Lockwood et al. 2002). In SMM, Clogg test has the greatest power and the most accurate Type I error rates when both *a* and *b* are zero. However, the Clogg test suffers from high Type I error rates when *a* is nonzero and *b* is zero, which is similar to our study. The decrease of power values when a increases alone also could be seen in SMM. In MacKinnon's study, the Sobel test and the Clogg test need large sample size assumption to achieve satisfactory power.

2.1.4 Discussion

The main purpose of this work was to describe the multivariate mediational model with one mediator in a cross-sectional mediational study and derive the corresponding inferential test procedures for the indirect effect. Two parametric methods, ECLG-P and ESOB-P, which are extensions of the Clogg test and the Sobel test, and two bootstrap methods were proposed. Using simulations, Type I error rates and power rates were compared.

The results showed that, in the presence of the correlation between the predictor and the mediator, ECLG-P provided the maximum power and the most accurate Type I error rate. This test had very high Type I error rates only when the correlation between the predictor and the mediator was zero, and the regression coefficient of the mediator on the outcome controlling the predictor was nonzero. The situation is interpreted as no correlation between the predictor and the mediator, which is not plausible in practical mediational studies. The correlation between the predictor and mediator is one of the key requirements for a mediator. Without this correlation, the causal relationship will be failed to build in the first step before performing hypothesis test of the indirect effect. Researchers might examine the significance of that coefficient before doing the ECLG-P test. ESOB-P has lower power than ECLG-P but for a large sample size (500), ESOB-P showed satisfactory power in all situations. The performance of BS-II in power is between these two methods.

Including all of the outcomes in one mediational model could effectively control the Type I error rates. In the event of significant indirect effect in a multivariate mediational model, post-hoc analysis using univariate mediational models should be followed.

2.2 LONGITUDINAL MEDIATIONAL MODELS

2.2.1 An LMM in Terms of RCMs

An example of the mediational process in an LMM is depicted in Figure 3. Let Y_i, the outcome of ith individual measured at four time occasions ($t_{i1}^{y}, t_{i2}^{y}, t_{i3}^{y}, t_{i4}^{y}$), be denoted by $Y_{i1}, Y_{i2}, Y_{i3}, Y_{i4}$. Let Z_i be the mediator of ith individual measured at four time occasions ($t_{i1}^{z}, t_{i2}^{z}, t_{i3}^{z}, t_{i4}^{z}$), be denoted by $Z_{i1}, Z_{i2}, Z_{i3}, Z_{i4}$. Let X_i denotes a predictor for the individual i. In Figure 3, Y1, Y2, Y3 and Y4 denote the outcome values for time periods 1, 2, 3 and 4. Similarly, Z1, Z2, Z3 and Z4 denote the mediator values for time periods 1, 2, 3 and 4. The parameter η_1 represents latent construct: initial status of the longitudinally observed mediator values and η_2 represents latent construct: the growth rate of the longitudinally observed mediator values. Similarly η_3 represents the latent construct: the initial status of the longitudinally observed outcome variables and η_4 represents the latent construct, the corresponding growth rate. Data could be irregularly acquired for different subjects, i.e. t_{ij}^{z} might not equal to $t_{i'j}^{z}$, and t_{ij}^{y} might not equal to $t_{i'j}^{y}$ where $j = 1, 2, 3, 4$, $i = 1, 2, \ldots, n$, $i' = 1, 2, \ldots, n$ and $i \neq i'$. However, $t_{i1}^{z}, t_{i2}^{z}, t_{i3}^{z}, t_{i4}^{z}$ are required to be temporally earlier than $t_{i1}^{y}, t_{i2}^{y}, t_{i3}^{y}, t_{i4}^{y}$.

With reference to Figure 3, equations 1.1 to 1.3 could be recast as multilevel equations in LMM as shown in Table 7 where $T^{y} = \begin{bmatrix} 1 & t_{i1}^{y} \\ 1 & t_{i2}^{y} \\ 1 & t_{i3}^{y} \\ 1 & t_{i4}^{y} \end{bmatrix}$ and $T^{z} = \begin{bmatrix} 1 & t_{i1}^{z} \\ 1 & t_{i2}^{z} \\ 1 & t_{i3}^{z} \\ 1 & t_{i4}^{z} \end{bmatrix}$.

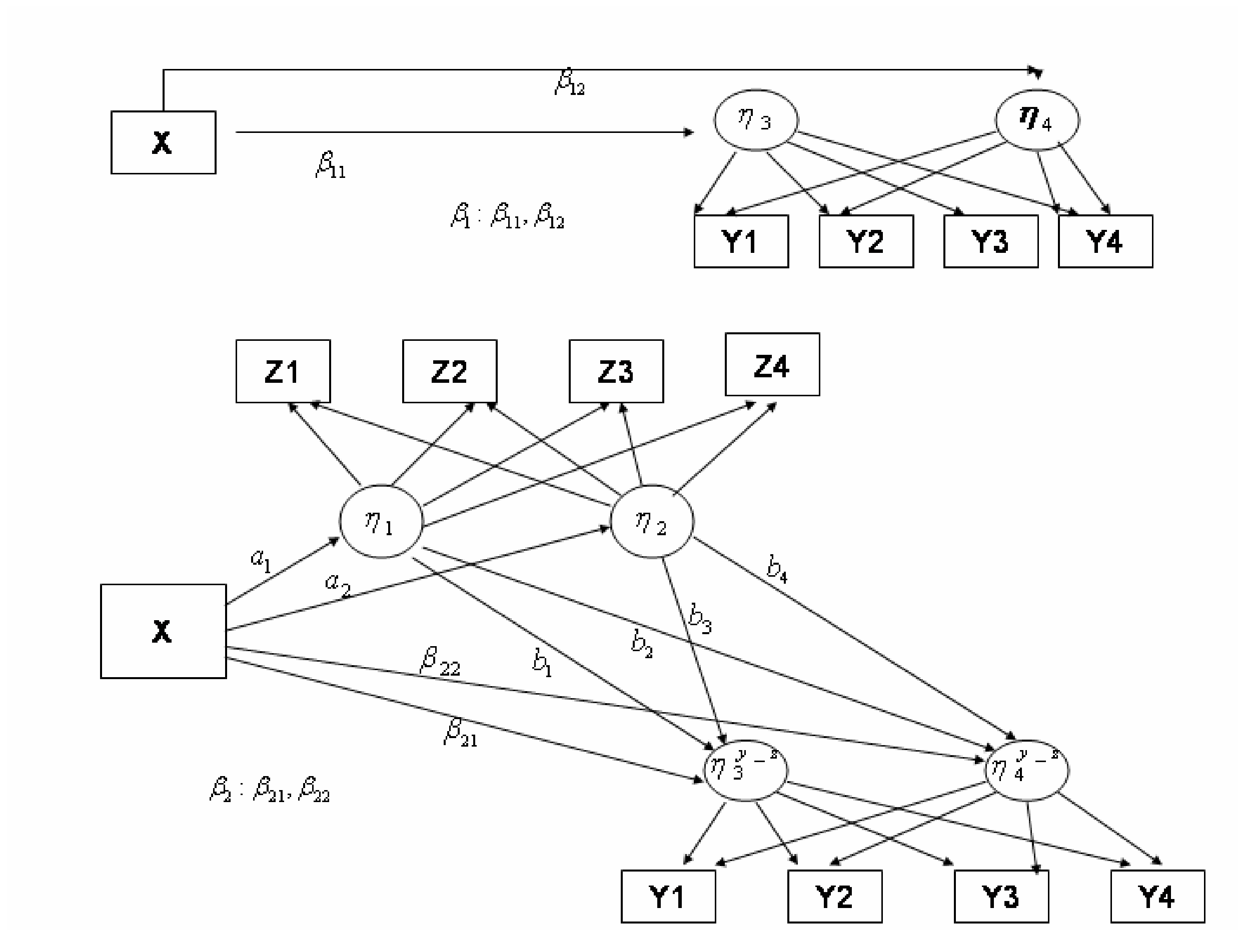


Fig 3. A longitudinal mediational model

Variables and the latent constructs are linked by arrows
X= predictor;
Y1, Y2, Y3, Y4 = a longitudinal outcome measured at four time points;
Z1, Z2, Z3, Z4 = a longitudinal mediator measured at four time points;
η_1 = initial status of mediator; η_2 = growth rate of mediator;
η_3 = initial status of outcome; η_4 = growth rate of outcome;
η_3^{y-z} = initial status of the outcome, accounting for η_1 and η_2;
η_4^{y-z} = growth rate of the outcome, accounting for η_1 and η_2;
β_{11}, β_{12}, β_{21}, β_{22}, a_1, a_2, b_1, b_2, b_3, b_4 = fixed effect parameters

Table 7. Multilevel equations for a mediational analysis

Outcome		
Level I model	$Y_i = T^y \eta_i^y + \varepsilon_i$	(2.4)
Level II model	$\eta_i^y = \begin{bmatrix} \eta_{3i} \\ \eta_{4i} \end{bmatrix} = \begin{bmatrix} \pi_0^y \\ \pi_1^y \end{bmatrix} + \begin{bmatrix} \beta_{11} \\ \beta_{12} \end{bmatrix} X_i + \begin{bmatrix} D_0^y \\ D_1^y \end{bmatrix}$	(2.5)
Mediator		
Level I model	$Z_i = T^z \eta_i^z + \xi_i$	(2.6)
Level II model	$\eta_i^z = \begin{bmatrix} \eta_{1i} \\ \eta_{2i} \end{bmatrix} = \begin{bmatrix} \pi_0^z \\ \pi_1^z \end{bmatrix} + \begin{bmatrix} a_1 \\ a_2 \end{bmatrix} X_i + \begin{bmatrix} D_0^z \\ D_1^z \end{bmatrix}$	(2.7)
Outcome accounting for mediators		
Level I model	$Y_i = T^y \eta_i^{y-z} + \upsilon_i^y$	(2.8)
Level II model	$\eta_i^{y-z} = \begin{bmatrix} \eta_{3i}^{y-z} \\ \eta_{4i}^{y-z} \end{bmatrix} = \begin{bmatrix} \pi_0^{y-z} \\ \pi_1^{y-z} \end{bmatrix} + \begin{bmatrix} \beta_{21} \\ \beta_{22} \end{bmatrix} X_i + \begin{bmatrix} b_1 & b_3 \\ b_2 & b_4 \end{bmatrix} \begin{bmatrix} \eta_{1i} \\ \eta_{2i} \end{bmatrix} + \begin{bmatrix} D_0^{y-z} \\ D_1^{y-z} \end{bmatrix}$	(2.9)

Substituting Level II equations (2.5, 2.7 and 2.9) into Level I equations (2.4, 2.6 and 2.8), the equations for random coefficient models are obtained as given below:

$$Y_{ij} = \pi_0^y + \pi_1^y t_{ij}^y + \beta_{11} X_i + \beta_{12} X_i t_{ij}^y + D_{0i}^y + D_{1i}^y t_{ij}^y + \varepsilon_{ij} \tag{2.10}$$

$$Z_{ij} = \pi_0^z + \pi_1^z t_{ij}^z + a_1 X_i + a_2 X_i t_{ij}^z + D_{0i}^z + D_{1i}^z t_{ij}^z + \xi_{ij} \tag{2.11}$$

$$\begin{aligned} Y_{ij} = {} & \pi_0^{y-z} + \pi_1^{y-z} t_{ij}^y + \beta_{21} X_i + \beta_{22} X_i t_{ij}^y + b_1 \eta_{1i} + b_3 \eta_{2i} + b_2 \eta_{1i} t_{ij}^y \\ & + b_4 \eta_{2i} t_{ij}^y + D_{0i}^{y-z} + D_{1i}^{y-z} t_{ij}^y + \upsilon_{ij} \end{aligned} \tag{2.12}$$

Substituting equation 2.7 into equation 2.12 yields:

$$\begin{aligned} Y_{ij} = {} & \pi_0^{y-z} + b_1 \pi_0^z + b_3 \pi_1^z + (\pi_1^{y-z} + b_2 \pi_0^z + b_4 \pi_1^z) t_{ij}^y + \\ & (\beta_{21} + a_1 b_1 + a_2 b_3) X_i + (\beta_{22} + a_1 b_2 + a_2 b_4) X_i t_{ij}^y + \\ & b_1 D_{0i}^z + b_3 D_{1i}^z + b_2 D_{0i}^z t_{ij}^y + b_4 D_{1i}^z t_{ij}^y + D_{0i}^{y-z} + D_{1i}^{y-z} t_{ij}^y + \upsilon_{ij} \end{aligned} \tag{2.13}$$

The residuals in the Level II models are called “random effects” in the RCMs. The coefficients vector $\beta_1 = (\beta_{11}, \beta_{12})$ represents the total effect of X on the intercept and slope (latent constructs) of the longitudinal outcome *Y*, and $\beta_2 = (\beta_{21}, \beta_{22})$ represents the direct effect of *X* on the intercept and the slope (latent constructs) of longitudinal *Y* accounting for the intercept and slope (latent constructs) of the longitudinal mediator *Z*. We first fit equation 2.11 and obtain the point estimates $\hat{a}_1$, $\hat{a}_2$, $\hat{D}_0^z$, $\hat{D}_1^z$ and $\hat{\sigma}_{\hat{a}}^2$.

Substituting these estimates into equation 2.13 we get:

$$\begin{aligned} Y_{ij} = {} & \pi_0^{y-z} + b_1\hat{\pi}_0^z + b_3\hat{\pi}_1^z + (\pi_1^{y-z} + b_2\hat{\pi}_0^z + b_4\hat{\pi}_1^z)t_{ij}^y + \\ & (\beta_{21} + \hat{a}_1 b_1 + \hat{a}_2 b_3)X_i + (\beta_{22} + \hat{a}_1 b_2 + \hat{a}_2 b_4)X_i t_{ij}^y + \\ & b_1\hat{D}_{0i}^z + b_3\hat{D}_{1i}^z + b_2\hat{D}_{0i}^z t_{ij}^y + b_4\hat{D}_{1i}^z t_{ij}^y + D_{0i}^{y-z} + D_{1i}^{y-z} t_{ij}^y + \upsilon_{ij} \end{aligned} \quad (2.14)$$

We rewrite equation 2.14 as :

$$\begin{aligned} Y_{ij} = {} & \delta_0 + \delta_1 t_{ij}^y + \delta_2 X_i + \delta_3 X_i t_{ij}^y + b_1\hat{D}_{0i}^z + b_3\hat{D}_{1i}^z + \\ & b_2\hat{D}_{0i}^z t_{ij}^y + b_4\hat{D}_{1i}^z t_{ij}^y + D_{0i}^{y-z} + D_{1i}^{y-z} t_{ij}^y + \upsilon_{ij} \end{aligned} \quad (2.15)$$

The point estimates of interest $\hat{b}_1$, $\hat{b}_2$, $\hat{b}_3$, $\hat{b}_4$ and $\hat{\sigma}_{\hat{b}}^2$ are obtained by fitting the equation 2.15.

2.2.2 Inferential Procedures

In a multiple mediational model with single outcome, Preacher and Hayes (Preacher and Hayes 2005) termed the indirect effect of the predictor on the outcome through all the mediators as *total indirect effect* to differ from the specific indirect effects of individual paths. Preacher and Hayes designed a B matrix with point estimates of the direct effects linking one predictor, multiple mediators, and one univariate outcome. The total effect is given by $\mathrm{T} = (\mathrm{I} - \mathrm{B})^{-1} - \mathrm{I}$ where I is an identity matrix and the total indirect effect is given by $\mathrm{F} = (\mathrm{I} - \mathrm{B})^{-1} - \mathrm{I} - \mathrm{B}$ (Bollen 1987). Preacher and Hayes (Preacher and Hayes 2005) also derived the first-order standard error of the point estimate of the total indirect effect based on multivariate delta method. The ratio of the point estimate and the standard error is compared to the standard normal critical values for the test of no total indirect effect.

In the proposed LMM, the longitudinal outcome and mediator variables consist of two components: the intercept and the growth factor, presented by two latent variables. Preacher and Hayes's approach with the corresponding notations, has been adopted in the present paper with one predictor (*X*), two latent variables (η_1 and η_2) for the longitudinally observed mediator, and two latent variables (η_3 and η_4) for the longitudinally observed outcome (See Figure 3). The total indirect effect of the predictor is defined as the effect of the predictor on the initial status and the growth rate of the outcome after accounting for the mediating effect of the initial status and the growth rate of the mediator. In what follows next, we adopted the notations of Preacher and Hayes (2005). Referring to Figure 3, the B matrix links two latent variables of the outcome

(η_1 and η_2), two latent variables of the mediator (η_3 and η_4), and the predictor (X), and is written as:

$$B = \begin{array}{c} \\ X \\ \eta_1 \\ \eta_2 \\ \eta_3 \\ \eta_4 \end{array} \begin{array}{c} \begin{array}{ccccc} X & \eta_1 & \eta_2 & \eta_3 & \eta_4 \end{array} \\ \begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ a_1 & 0 & 0 & 0 & 0 \\ a_2 & 0 & 0 & 0 & 0 \\ \beta_{21} & b_1 & b_3 & 0 & 0 \\ \beta_{22} & b_2 & b_4 & 0 & 0 \end{bmatrix} \end{array}$$

The indirect effect is given as $\mathrm{F} = (\mathrm{I} - \mathrm{B})^{-1} - \mathrm{I} - \mathrm{B}$:

$$F = \begin{array}{c} \\ X \\ \eta_1 \\ \eta_2 \\ \eta_3 \\ \eta_4 \end{array} \begin{array}{c} \begin{array}{ccccc} X & \eta_1 & \eta_2 & \eta_3 & \eta_4 \end{array} \\ \begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ a_1 b_1 + a_2 b_3 & 0 & 0 & 0 & 0 \\ a_1 b_2 + a_2 b_4 & 0 & 0 & 0 & 0 \end{bmatrix} \end{array}.$$

Let f be the matrix with differentiable elements of F. The point estimate of the total indirect effect (f) is

$$\hat{\mathrm{f}} = \begin{bmatrix} \hat{\mathrm{f}}_1 \\ \hat{\mathrm{f}}_2 \end{bmatrix} = \begin{bmatrix} \hat{a}_1 \hat{b}_1 + \hat{a}_2 \hat{b}_3 \\ \hat{a}_1 \hat{b}_2 + \hat{a}_2 \hat{b}_4 \end{bmatrix} \tag{2.16}$$

from the invariance property of the maximum likelihood estimators (Zehna 1966).

Let θ' be the unknown parameter vector, $(a_1 \ a_2 \ b_1 \ b_2 \ b_3 \ b_4)$. For large sample size, the estimate of asymptotic variance covariance matrix of this total indirect effect evaluated at $\hat{\theta}$ (m.l.e of θ) is given by

$$\hat{V}(\hat{\mathrm{f}}) = N^{-1}\left[\left(\frac{\partial \mathrm{f}}{\partial \hat{\theta}}\right)' V(\hat{\theta})\left(\frac{\partial \mathrm{f}}{\partial \hat{\theta}}\right)\right] \tag{2.17}$$

where $\left(\frac{\partial \mathrm{f}}{\partial \hat{\theta}}\right)' = \begin{bmatrix} \hat{b}_1 & \hat{b}_3 & \hat{a}_1 & 0 & \hat{a}_2 & 0 \\ \hat{b}_2 & \hat{b}_4 & 0 & \hat{a}_1 & 0 & \hat{a}_2 \end{bmatrix}$.

Assuming (D_0^z, D_1^z) and (D_0^{y-z}, D_1^{y-z}) to be uncorrelated,

$$N^{-1}\hat{V}(\hat{\theta}) = \begin{bmatrix} \hat{\sigma}^2_{\hat{a}_1} & \hat{\sigma}_{\hat{a}_1\hat{a}_2} & 0 & 0 & 0 & 0 \\ \hat{\sigma}_{\hat{a}_1\hat{a}_2} & \hat{\sigma}^2_{\hat{a}_2} & 0 & 0 & 0 & 0 \\ 0 & 0 & \hat{\sigma}^2_{\hat{b}_1} & \hat{\sigma}_{\hat{b}_1\hat{b}_2} & \hat{\sigma}_{\hat{b}_1\hat{b}_3} & \hat{\sigma}_{\hat{b}_1\hat{b}_4} \\ 0 & 0 & \hat{\sigma}_{\hat{b}_1\hat{b}_2} & \hat{\sigma}^2_{\hat{b}_2} & \hat{\sigma}_{\hat{b}_1\hat{b}_4} & \hat{\sigma}_{\hat{b}_2\hat{b}_4} \\ 0 & 0 & \hat{\sigma}_{\hat{b}_1\hat{b}_3} & \hat{\sigma}_{\hat{b}_2\hat{b}_3} & \hat{\sigma}^2_{\hat{b}_3} & \hat{\sigma}_{\hat{b}_3\hat{b}_4} \\ 0 & 0 & \hat{\sigma}_{\hat{b}_1\hat{b}_4} & \hat{\sigma}_{\hat{b}_2\hat{b}_4} & \hat{\sigma}_{\hat{b}_3\hat{b}_4} & \hat{\sigma}^2_{\hat{b}_4} \end{bmatrix}, \tag{2.18}$$

and

$$\hat{V}(\hat{\mathrm{f}}) = \begin{bmatrix} \hat{V}(\mathrm{f}_1) & \hat{V}(\mathrm{f}_1, \mathrm{f}_2) \\ \hat{V}(\mathrm{f}_1, \mathrm{f}_2) & \hat{V}(\mathrm{f}_2) \end{bmatrix} \tag{2.19}$$

where $\hat{V}(\mathrm{f}_1) = \hat{b}_1^2\hat{\sigma}^2_{\hat{a}_1} + 2\hat{b}_1\hat{b}_3\hat{\sigma}_{\hat{a}_1\hat{a}_2} + \hat{b}_3^2\hat{\sigma}^2_{\hat{a}_2} + \hat{a}_1^2\hat{\sigma}^2_{\hat{b}_1} + 2\hat{a}_1\hat{a}_2\hat{\sigma}_{\hat{b}_1\hat{b}_3} + \hat{a}_2^2\hat{\sigma}^2_{\hat{b}_3}$;

$$\begin{aligned} \hat{V}(\mathrm{f}_1, \mathrm{f}_2) = {} & \hat{b}_1\hat{b}_2\hat{\sigma}^2_{\hat{a}_1} + (\hat{b}_2\hat{b}_3 + \hat{b}_1\hat{b}_4)\hat{\sigma}_{\hat{a}_1\hat{a}_2} + \hat{b}_3\hat{b}_4\hat{\sigma}^2_{\hat{a}_2} + \hat{a}_1^2\hat{\sigma}_{\hat{b}_1\hat{b}_2} \\ & + \hat{a}_1\hat{a}_2(\hat{\sigma}_{\hat{b}_1\hat{b}_4} + \hat{\sigma}_{\hat{b}_2\hat{b}_3}) + \hat{a}_2^2\hat{\sigma}_{\hat{b}_3\hat{b}_4} \end{aligned};$$

and $\hat{V}(\mathrm{f}_2) = \hat{b}_2^2\hat{\sigma}^2_{\hat{a}_1} + 2\hat{b}_2\hat{b}_4\hat{\sigma}_{\hat{a}_1\hat{a}_2} + \hat{b}_4^2\hat{\sigma}^2_{\hat{a}_2} + \hat{a}_1^2\hat{\sigma}^2_{\hat{b}_2} + 2\hat{a}_1\hat{a}_2\hat{\sigma}_{\hat{b}_2\hat{b}_4} + \hat{a}_2^2\hat{\sigma}^2_{\hat{b}_4}$

The estimates $\hat{a}_1, \hat{a}_2, \hat{b}_1, \hat{b}_2, \hat{b}_3, \hat{b}_4$ and the estimated covariance matrix are obtained by fitting equations 2.11 and 2.15 using the residual maximum likelihood (REML) method given by SAS (Version 9.19). The hypothesis of the total indirect effect can be tested by $T = \hat{f}'[\hat{V}(\hat{f})]^{-1}\hat{f}$, which can be compared to the critical values of *Chi-square* distribution with degrees of freedom 2.

In SMM, the product of the two coefficients does not always follow a standard normal distribution. Therefore, the Sobel test requires large sample size to conduct the test of the indirect effect (Preacher and Hayes 2004). An alternative is to use bootstrap approaches (MacKinnon, Lockwood et al. 2004). Similarly, in LMM, a nonparametric bootstrap approach is required to avoid the large sample size assumption. It is straightforward to extend the bootstrap method, BS-I (section 2.1.1) to test the total indirect effect in LMM. Let $\Sigma = \text{var}(f)$, be the variance covariance matrix of the point estimate of the total indirect effect, f . The Bootstrap method consists of the following steps:

1) Calculate the $\hat{f}$, $\hat{\Sigma}$ and $\hat{T} = \hat{f}\hat{\Sigma}^{-1}\hat{f}'$ from observed data using the method we described.
2) Repeatedly sample with replacement from the observed data to generate *B* bootstrap samples. Let $\hat{f}_i^*$ and $\hat{\Sigma}_i^*$ denote the bootstrap versions of $\hat{f}$ and $\hat{\Sigma}$, calculated from the *i*th bootstrap sample, $i, = 1,2.....B$. Then calculate $\hat{T}_i^* = (\hat{f} - \hat{f}_i^*)\hat{\Sigma}_i^{*-1}(\hat{f}' - \hat{f}_i^*{}')$.
3) Use the $\frac{\alpha}{2}$ th and $(1-\frac{\alpha}{2})$ th percentiles of the bootstrap distribution of $\hat{T}^*$ to obtain the "bootstrap critical interval" ($\hat{T}^*_{\frac{\alpha}{2}}$, $\hat{T}^*_{1-\frac{\alpha}{2}}$).
4) The rejection of the null hypothesis is failed if $\hat{T}^*_{\frac{\alpha}{2}} < \hat{T} < \hat{T}^*_{1-\frac{\alpha}{2}}$.

2.2.3 Monte Carlo Study

Study Design

The purpose of this Monte Carlo study is to investigate the accuracy of the estimates and the performance (Type I error rates and power rates) for the proposed method.

The SAS programming language was used to generate multilevel data sets, reflecting the mediational relationship between a predictor (*X*), a longitudinally mediator (*M*), and a longitudinally outcome (*Y*). Sample sizes were chosen as 50, 100, 200, and 500. The data sets were comprised of the level II subjects (i=1, 2,…n; n=50, 100, 200, and 500) with 10 Level I observations (j=1,2…10) per subject. Therefore, there were 500, 1000, 2000, and 5000 observations corresponding to sample size groups of 50, 100, 200, and 500. Predicator *X* was first set to a binary variable representing the two groups, half of the subjects were assumed at random 0s, and the other half were similarly assigned 1s at random. Next, *X* was simulated from a standard normal distribution representing a continuous predictor. The time points for the mediator (t_{ij}^{z}) was set to 1 to 10, and the time points for the outcome (t_{ij}^{y}) was set to 16 to 25.

Three combinations were simulated corresponding to small, moderate, and high level of residual variances in equation 2.11 and 2.15. All the residuals of level I models and Level II models were simulated from a multivariate normal distribution with mean zeros. The set of residuals is compromised of the random effect of the intercept (D_{0i}^{z}), the random effect of the slope (D_{1i}^{z}), and ξ_{ij} in equation 2.11; and the random effect of the intercept (D_{0i}^{y-z}), the random effect of the slope (D_{1i}^{y-z}), and υ_{ij} in equation 2.15. Their variances were shown in Table 8.

Table 8. Small, moderate, and high residual variances for the simulation study

	Level II Residual Variances		Level I Residual Variances	
	$\begin{bmatrix} \sigma^2_{D_0^z} & \sigma_{D_{01}^z} \\ \sigma_{D_{01}^z} & \sigma^2_{D_1^z} \end{bmatrix}$	$\begin{bmatrix} \sigma^2_{D_0^{y-z}} & \sigma_{D_{01}^{y-z}} \\ \sigma_{D_{01}^{y-z}} & \sigma^2_{D_1^{y-z}} \end{bmatrix}$	$\sigma^2_{\xi_{ij}}$	$\sigma^2_{\upsilon_{ij}}$
Small	$\begin{bmatrix} .05 & .01 \\ .01 & .05 \end{bmatrix}$	$\begin{bmatrix} .05 & .01 \\ .01 & .05 \end{bmatrix}$	0.05	0.05
Moderate	$\begin{bmatrix} .25 & .05 \\ .05 & .25 \end{bmatrix}$	$\begin{bmatrix} .25 & .05 \\ .05 & .25 \end{bmatrix}$	0.25	0.25
High	$\begin{bmatrix} 1 & .2 \\ .2 & 1 \end{bmatrix}$	$\begin{bmatrix} 1 & .2 \\ .2 & 1 \end{bmatrix}$	1	1

The fixed effects parameters were set as follows: $\pi_0^z = \pi_1^z = \pi_0^y = \pi_1^y = 0.3$; $\beta_{21} = \beta_{22} = 0.2$. Let a_s and b_s be the component of vector *a* and matrix *b*. We varied values of total indirect effect by changing a_s and b_s specifically, where a_s was chosen to be 0, 0.3, and 0.6, and b_s were set to 0, 0.1, and 0.4. Therefore, the true values of the total indirect effect were (0, 0), (0.12, 0.12), (0.24, 0.24), and (0.48, 0.48). In this thesis, we only focus on positive regression coefficients for simplicity.

We calculated Z_{ij} from equation 2.11. Using the same D_{0i}^z and D_{1i}^z as used in 2.11, the outcome Y_{ij} was calculated from equation 2.14 with all the parameters we described.

Using SAS PROC MIXED, we fit equation 2.11 to get $\hat{a}_1$, $\hat{a}_2$, $\hat{D}_{0i}^z$, $\hat{D}_{1i}^z$, and the variance-covariance of $\hat{a}$. Fitting equation 2.15 with these estimates, we obtained the estimates $\hat{b}_1$, $\hat{b}_2$, $\hat{b}_3$, $\hat{b}_4$ and variance-covariance of $\hat{b}$. The point estimate of the total indirect effect as well as the approximate variance-covariance matrix were calculated by equation 2.16 and 2.17, followed with the hypothesis test. The parameters described in the simulation were used in the previous studies (Krull and MacKinnon 2001; MacKinnon, Lockwood et al. 2002; Bauer, Preacher et al. 2006).

For each of the 144 conditions, 500 data sets were created in the SAS (Version 9.13) programming language. The accuracy of the point estimates were evaluated by the bias. For point estimate of the total indirect effect, bias was obtained from the difference between the average of the estimates and the true parameters value. To determine the bias of variance-covariance of the estimate of the total indirect effect, we compared average variance with sample variance, where the average variance is the mean of the variance-covariance calculated from each simulated dataset and the sample variance is the variance of the estimates of the total indirect effect. The sample variance were treated as the true parameters to evaluate the accuracy of the average variance.

The proportion of replications rejecting the null hypothesis of no total indirect effect provided an estimate of the Type I error rate and statistical power, which is shown as percentages in Table 15 and 16. We used the 5% (of 500 replications) significant level. As discussed in section 2.1.3, the indirect effects are expected to be statistically significant in 25 of the 500 samples when b equals zero. In this simulation study, we only use positive regression coefficients parameters for simplicity. In practical studies, a could hardly be zero because one of the requirements for a mediator is that the correlation between the predictor and the mediator exists. When ab is not equals zero, the percentages provided the measure of statistical power.

Simulation Results

Accuracy of the point estimates were evaluated by the bias. The point estimates of the total indirect effect were essentially unbiased in all conditions, which were not shown in the thesis. As shown in Table 9 to 14, the bias of the average variances decreased as the sample size increased. Overall, the proposed method provided a reliable estimate for the variance covariance of the total indirect effect except for small sample size conditions.

Type I error rates (the first two rows) and the empirical power rates (the last four rows) were shown as percentages in Table 15 and 16 for different magnitudes of the residual variance. The tables were organized to represent the rejection rates in different combinations of *a* and *b*.

Evaluation of the Type I error rate was performed when *b* alone was zero. In binary predictor cases (Table 15), the Type I error rates were around nominal (5%) value in all situations excepting *a* was high (0.6) in very small sample size (50) with small residual variance. In continuous predictor cases with small residual variance (Table 16), the method overestimated the Type I error rates. In addition, the Type I error rates were higher than 5% in the presence of moderate residual variance when *a* was high. When sample size achieves 500, the method had reliable Type I error rate.

As expected, the power values increased as sample size increased and the residual variance decreased. The power values were more sensitive to values of *b* than *a*. When *b* was small (0.1), the method had unsatisfactory power (less than 0.8) in most cases. Compared with binary predictor (Table 15), the power values were larger in continuous predictor conditions (Table 16), especially for high residual variance. For a large sample size (500), when the predictor was binary, the method showed satisfactory power in all but one condition where both *a* and *b* were small with large residual variance. When the predictor was continuous, the method showed satisfactory power in all situations.

Table 9. Variances of the total indirect effect with small residual variance when the predictor (*X*) is binary

Parameter	Sample size *n=50*;		Sample size *n=100*;		Sample size *n=200*;		Sample size *n=500*;	
	Average Variance	Sample Variance	Average Variance	Sample Variance	Average Variance	Sample Variance	Average Variance	Sample Variance
a_s =.3; b_s =0	$\begin{bmatrix} .003 & . \\ 0 & .004 \end{bmatrix}$	$\begin{bmatrix} .003 & . \\ 0 & .004 \end{bmatrix}$	$\begin{bmatrix} .012 & . \\ 0 & .002 \end{bmatrix}$	$\begin{bmatrix} .011 & . \\ 0 & .002 \end{bmatrix}$	$\begin{bmatrix} .006 & . \\ 0 & 0 \end{bmatrix}$	$\begin{bmatrix} .006 & . \\ 0 & 0 \end{bmatrix}$	$\begin{bmatrix} .002 & . \\ 0 & 0 \end{bmatrix}$	$\begin{bmatrix} .002 & . \\ 0 & 0 \end{bmatrix}$
a_s =.6; b_s =0	$\begin{bmatrix} .099 & . \\ -.001 & .016 \end{bmatrix}$	$\begin{bmatrix} .108 & . \\ -.001 & .018 \end{bmatrix}$	$\begin{bmatrix} .044 & . \\ 0 & .007 \end{bmatrix}$	$\begin{bmatrix} .040 & . \\ 0 & .007 \end{bmatrix}$	$\begin{bmatrix} .022 & . \\ 0 & .003 \end{bmatrix}$	$\begin{bmatrix} .022 & . \\ 0 & .003 \end{bmatrix}$	$\begin{bmatrix} .008 & . \\ 0 & .001 \end{bmatrix}$	$\begin{bmatrix} .008 & . \\ 0 & .001 \end{bmatrix}$
a_s =.3; b_s =.1	$\begin{bmatrix} .029 & . \\ 0 & .005 \end{bmatrix}$	$\begin{bmatrix} .030 & . \\ 0 & .005 \end{bmatrix}$	$\begin{bmatrix} .012 & . \\ 0 & .002 \end{bmatrix}$	$\begin{bmatrix} .013 & . \\ 0 & .002 \end{bmatrix}$	$\begin{bmatrix} .006 & . \\ 0 & .001 \end{bmatrix}$	$\begin{bmatrix} .006 & . \\ 0 & .001 \end{bmatrix}$	$\begin{bmatrix} .002 & . \\ 0 & 0 \end{bmatrix}$	$\begin{bmatrix} .002 & . \\ 0 & 0 \end{bmatrix}$
a_s =.3; b_s =.4	$\begin{bmatrix} .029 & . \\ .002 & .006 \end{bmatrix}$	$\begin{bmatrix} .028 & . \\ .002 & .007 \end{bmatrix}$	$\begin{bmatrix} .013 & . \\ 0 & .003 \end{bmatrix}$	$\begin{bmatrix} .016 & . \\ .001 & .003 \end{bmatrix}$	$\begin{bmatrix} .006 & . \\ 0 & .001 \end{bmatrix}$	$\begin{bmatrix} .006 & . \\ 0 & .001 \end{bmatrix}$	$\begin{bmatrix} .002 & . \\ 0 & .001 \end{bmatrix}$	$\begin{bmatrix} .002 & . \\ 0 & .001 \end{bmatrix}$
a_s =.6; b_s =.1	$\begin{bmatrix} .096 & . \\ 0 & .016 \end{bmatrix}$	$\begin{bmatrix} .105 & . \\ 0 & .016 \end{bmatrix}$	$\begin{bmatrix} .044 & . \\ 0 & .008 \end{bmatrix}$	$\begin{bmatrix} .047 & . \\ 0 & .008 \end{bmatrix}$	$\begin{bmatrix} .022 & . \\ 0 & .004 \end{bmatrix}$	$\begin{bmatrix} .023 & . \\ 0 & .004 \end{bmatrix}$	$\begin{bmatrix} .008 & . \\ 0 & .001 \end{bmatrix}$	$\begin{bmatrix} .008 & . \\ 0 & .001 \end{bmatrix}$
a_s =.6; b_s =.4	$\begin{bmatrix} .101 & . \\ .001 & .018 \end{bmatrix}$	$\begin{bmatrix} .105 & . \\ .001 & .020 \end{bmatrix}$	$\begin{bmatrix} .046 & . \\ 0 & .009 \end{bmatrix}$	$\begin{bmatrix} .056 & . \\ 0 & .009 \end{bmatrix}$	$\begin{bmatrix} .023 & . \\ 0 & .004 \end{bmatrix}$	$\begin{bmatrix} .024 & . \\ 0 & .004 \end{bmatrix}$	$\begin{bmatrix} .009 & . \\ 0 & .002 \end{bmatrix}$	$\begin{bmatrix} .009 & . \\ 0 & .002 \end{bmatrix}$

Table 10. Variances of the total indirect effect with moderate residual variance when the predictor (*X*) is binary

Parameter	Sample size *n=50*;		Sample size *n=100*;		Sample size *n=200*;		Sample size *n=500*;	
	Average Variance	Sample Variance	Average Variance	Sample Variance	Average Variance	Sample Variance	Average Variance	Sample Variance
a_s =.3; b_s =0	$\begin{bmatrix} .042 & . \\ 0 & .007 \end{bmatrix}$	$\begin{bmatrix} .034 & . \\ 0 & .007 \end{bmatrix}$	$\begin{bmatrix} .016 & . \\ 0 & .003 \end{bmatrix}$	$\begin{bmatrix} .014 & . \\ 0 & .003 \end{bmatrix}$	$\begin{bmatrix} .002 & . \\ 0 & 0 \end{bmatrix}$	$\begin{bmatrix} .002 & . \\ 0 & 0 \end{bmatrix}$	$\begin{bmatrix} .002 & . \\ 0 & 0 \end{bmatrix}$	$\begin{bmatrix} .002 & . \\ 0 & 0 \end{bmatrix}$
a_s =.6; b_s =0	$\begin{bmatrix} .117 & . \\ .001 & .018 \end{bmatrix}$	$\begin{bmatrix} .106 & . \\ .002 & .019 \end{bmatrix}$	$\begin{bmatrix} .048 & . \\ 0 & .008 \end{bmatrix}$	$\begin{bmatrix} .048 & . \\ 0 & .008 \end{bmatrix}$	$\begin{bmatrix} .009 & . \\ 0 & .001 \end{bmatrix}$	$\begin{bmatrix} .009 & 0 \\ 0 & .001 \end{bmatrix}$	$\begin{bmatrix} .009 & . \\ 0 & .001 \end{bmatrix}$	$\begin{bmatrix} .009 & . \\ 0 & .001 \end{bmatrix}$
a_s =.3; b_s =.1	$\begin{bmatrix} .053 & . \\ 0 & .010 \end{bmatrix}$	$\begin{bmatrix} .038 & . \\ 0 & .008 \end{bmatrix}$	$\begin{bmatrix} .016 & . \\ 0 & .003 \end{bmatrix}$	$\begin{bmatrix} .014 & . \\ 0 & .003 \end{bmatrix}$	$\begin{bmatrix} .002 & . \\ 0 & 0 \end{bmatrix}$	$\begin{bmatrix} .002 & 0 \\ 0 & 0 \end{bmatrix}$	$\begin{bmatrix} .002 & . \\ 0 & 0 \end{bmatrix}$	$\begin{bmatrix} .002 & . \\ 0 & 0 \end{bmatrix}$
a_s =.3; b_s =.4	$\begin{bmatrix} .052 & . \\ .010 & .016 \end{bmatrix}$	$\begin{bmatrix} .049 & . \\ .010 & .016 \end{bmatrix}$	$\begin{bmatrix} .020 & . \\ .004 & .007 \end{bmatrix}$	$\begin{bmatrix} .019 & . \\ .004 & .007 \end{bmatrix}$	$\begin{bmatrix} .003 & . \\ 0 & .001 \end{bmatrix}$	$\begin{bmatrix} .003 & 0 \\ 0 & .001 \end{bmatrix}$	$\begin{bmatrix} .003 & . \\ .001 & .001 \end{bmatrix}$	$\begin{bmatrix} .003 & . \\ .001 & .001 \end{bmatrix}$
a_s =.6; b_s =.1	$\begin{bmatrix} .108 & . \\ 0 & .019 \end{bmatrix}$	$\begin{bmatrix} .115 & . \\ .002 & .018 \end{bmatrix}$	$\begin{bmatrix} .049 & . \\ 0 & .008 \end{bmatrix}$	$\begin{bmatrix} .047 & . \\ 0 & .007 \end{bmatrix}$	$\begin{bmatrix} .009 & . \\ 0 & .001 \end{bmatrix}$	$\begin{bmatrix} .010 & . \\ 0 & .001 \end{bmatrix}$	$\begin{bmatrix} .010 & . \\ 0 & .001 \end{bmatrix}$	$\begin{bmatrix} .010 & . \\ 0 & .001 \end{bmatrix}$
a_s =.6; b_s =.4	$\begin{bmatrix} .131 & . \\ .007 & .030 \end{bmatrix}$	$\begin{bmatrix} .132 & . \\ .019 & .030 \end{bmatrix}$	$\begin{bmatrix} .052 & . \\ .004 & .012 \end{bmatrix}$	$\begin{bmatrix} .048 & . \\ .004 & .013 \end{bmatrix}$	$\begin{bmatrix} .010 & . \\ 0 & .002 \end{bmatrix}$	$\begin{bmatrix} .010 & . \\ 0 & .002 \end{bmatrix}$	$\begin{bmatrix} .010 & . \\ 0 & .002 \end{bmatrix}$	$\begin{bmatrix} .010 & 0 \\ 0 & .002 \end{bmatrix}$

Table 11. Variances of the total indirect effect with high residual variance when the predictor (*X*) is binary

Parameter	Sample size *n=50*;		Sample size *n=100*;		Sample size *n=200*;		Sample size *n=500*;	
	Average Variance	Sample Variance	Average Variance	Sample Variance	Average Variance	Sample Variance	Average Variance	Sample Variance
a_s =.3; b_s =0	$\begin{bmatrix} .105 & . \\ .002 & .017 \end{bmatrix}$	$\begin{bmatrix} .073 & . \\ .004 & .015 \end{bmatrix}$	$\begin{bmatrix} .029 & . \\ 0 & .005 \end{bmatrix}$	$\begin{bmatrix} .021 & . \\ 0 & .003 \end{bmatrix}$	$\begin{bmatrix} .009 & . \\ 0 & .002 \end{bmatrix}$	$\begin{bmatrix} .007 & . \\ 0 & .001 \end{bmatrix}$	$\begin{bmatrix} .003 & . \\ 0 & 0 \end{bmatrix}$	$\begin{bmatrix} .003 & . \\ 0 & 0 \end{bmatrix}$
a_s =.6; b_s =0	$\begin{bmatrix} .172 & . \\ .002 & .027 \end{bmatrix}$	$\begin{bmatrix} .171 & . \\ .002 & .024 \end{bmatrix}$	$\begin{bmatrix} .059 & . \\ 0 & .010 \end{bmatrix}$	$\begin{bmatrix} .050 & . \\ 0 & .009 \end{bmatrix}$	$\begin{bmatrix} .026 & . \\ 0 & .004 \end{bmatrix}$	$\begin{bmatrix} .023 & . \\ 0 & .005 \end{bmatrix}$	$\begin{bmatrix} .010 & . \\ 0 & .001 \end{bmatrix}$	$\begin{bmatrix} .008 & . \\ 0 & .001 \end{bmatrix}$
a_s =.3; b_s =.1	$\begin{bmatrix} .101 & . \\ .003 & .019 \end{bmatrix}$	$\begin{bmatrix} .062 & . \\ .002 & .014 \end{bmatrix}$	$\begin{bmatrix} .028 & . \\ .001 & .006 \end{bmatrix}$	$\begin{bmatrix} .023 & . \\ .001 & .004 \end{bmatrix}$	$\begin{bmatrix} .010 & . \\ 0 & .002 \end{bmatrix}$	$\begin{bmatrix} .010 & . \\ 0 & .002 \end{bmatrix}$	$\begin{bmatrix} .003 & . \\ 0 & 0 \end{bmatrix}$	$\begin{bmatrix} .002 & . \\ 0 & 0 \end{bmatrix}$
a_s =.3; b_s =.4	$\begin{bmatrix} .123 & . \\ .032 & .052 \end{bmatrix}$	$\begin{bmatrix} .101 & . \\ .036 & .050 \end{bmatrix}$	$\begin{bmatrix} .046 & . \\ .018 & .023 \end{bmatrix}$	$\begin{bmatrix} .044 & . \\ .019 & .025 \end{bmatrix}$	$\begin{bmatrix} .018 & . \\ .009 & .010 \end{bmatrix}$	$\begin{bmatrix} .015 & . \\ .007 & .009 \end{bmatrix}$	$\begin{bmatrix} .006 & . \\ .003 & .004 \end{bmatrix}$	$\begin{bmatrix} .006 & . \\ .003 & .004 \end{bmatrix}$
a_s =.6; b_s =.1	$\begin{bmatrix} .160 & . \\ .001 & .029 \end{bmatrix}$	$\begin{bmatrix} .147 & . \\ .003 & .026 \end{bmatrix}$	$\begin{bmatrix} .060 & . \\ .001 & .011 \end{bmatrix}$	$\begin{bmatrix} .056 & . \\ .002 & .010 \end{bmatrix}$	$\begin{bmatrix} .026 & . \\ 0 & .005 \end{bmatrix}$	$\begin{bmatrix} .026 & . \\ 0 & .005 \end{bmatrix}$	$\begin{bmatrix} .009 & . \\ 0 & .002 \end{bmatrix}$	$\begin{bmatrix} .009 & . \\ 0 & .002 \end{bmatrix}$
a_s =.6; b_s =.4	$\begin{bmatrix} .202 & . \\ .035 & .063 \end{bmatrix}$	$\begin{bmatrix} .173 & . \\ .029 & .060 \end{bmatrix}$	$\begin{bmatrix} .079 & . \\ .017 & .028 \end{bmatrix}$	$\begin{bmatrix} .074 & . \\ .015 & .025 \end{bmatrix}$	$\begin{bmatrix} .030 & . \\ .007 & .012 \end{bmatrix}$	$\begin{bmatrix} .034 & . \\ .009 & .013 \end{bmatrix}$	$\begin{bmatrix} .013 & . \\ .004 & .005 \end{bmatrix}$	$\begin{bmatrix} .013 & . \\ .003 & .005 \end{bmatrix}$

Table 12. Variances of the total indirect effect with small residual variance when the predictor (*X*) is continuous

Parameter	Sample size *n=50*;		Sample size *n=100*;		Sample size *n=200*;		Sample size *n=500*;	
	Average Variance	Sample Variance	Average Variance	Sample Variance	Average Variance	Sample Variance	Average Variance	Sample Variance
$a_s=.3$; $b_s=0$	$\begin{bmatrix} .025 & . \\ 0 & .004 \end{bmatrix}$	$\begin{bmatrix} .026 & . \\ -.001 & .005 \end{bmatrix}$	$\begin{bmatrix} .011 & . \\ 0 & .002 \end{bmatrix}$	$\begin{bmatrix} .012 & . \\ 0 & .002 \end{bmatrix}$	$\begin{bmatrix} .005 & . \\ 0 & .002 \end{bmatrix}$	$\begin{bmatrix} .005 & . \\ 0 & .001 \end{bmatrix}$	$\begin{bmatrix} .002 & . \\ 0 & 0 \end{bmatrix}$	$\begin{bmatrix} .001 & . \\ 0 & 0 \end{bmatrix}$
$a_s=.6$; $b_s=0$	$\begin{bmatrix} .097 & . \\ -.001 & .016 \end{bmatrix}$	$\begin{bmatrix} .098 & . \\ -.005 & .018 \end{bmatrix}$	$\begin{bmatrix} .043 & . \\ 0 & .007 \end{bmatrix}$	$\begin{bmatrix} .045 & . \\ 0 & .008 \end{bmatrix}$	$\begin{bmatrix} .021 & . \\ 0 & .003 \end{bmatrix}$	$\begin{bmatrix} .022 & . \\ 0 & .004 \end{bmatrix}$	$\begin{bmatrix} .009 & . \\ 0 & .001 \end{bmatrix}$	$\begin{bmatrix} .009 & . \\ 0 & .001 \end{bmatrix}$
$a_s=.3$; $b_s=.1$	$\begin{bmatrix} .025 & . \\ 0 & .004 \end{bmatrix}$	$\begin{bmatrix} .029 & . \\ 0 & .004 \end{bmatrix}$	$\begin{bmatrix} .012 & . \\ 0 & .002 \end{bmatrix}$	$\begin{bmatrix} .012 & . \\ 0 & .002 \end{bmatrix}$	$\begin{bmatrix} .005 & 0 \\ 0 & .001 \end{bmatrix}$	$\begin{bmatrix} .005 & 0 \\ 0 & .001 \end{bmatrix}$	$\begin{bmatrix} .002 & . \\ 0 & 0 \end{bmatrix}$	$\begin{bmatrix} .002 & . \\ 0 & 0 \end{bmatrix}$
$a_s=.3$; $b_s=.4$	$\begin{bmatrix} .025 & . \\ 0 & .005 \end{bmatrix}$	$\begin{bmatrix} .032 & . \\ .001 & .005 \end{bmatrix}$	$\begin{bmatrix} .017 & . \\ 0 & .002 \end{bmatrix}$	$\begin{bmatrix} .013 & . \\ 0 & .002 \end{bmatrix}$	$\begin{bmatrix} .006 & . \\ 0 & .001 \end{bmatrix}$	$\begin{bmatrix} .006 & . \\ 0 & .001 \end{bmatrix}$	$\begin{bmatrix} .002 & . \\ 0 & 0 \end{bmatrix}$	$\begin{bmatrix} .002 & . \\ 0 & 0 \end{bmatrix}$
$a_s=.6$; $b_s=.1$	$\begin{bmatrix} .091 & . \\ -.001 & .015 \end{bmatrix}$	$\begin{bmatrix} .104 & . \\ -.002 & .017 \end{bmatrix}$	$\begin{bmatrix} .044 & . \\ 0 & .007 \end{bmatrix}$	$\begin{bmatrix} .045 & . \\ 0 & .007 \end{bmatrix}$	$\begin{bmatrix} .022 & . \\ 0 & .004 \end{bmatrix}$	$\begin{bmatrix} .023 & . \\ 0 & .004 \end{bmatrix}$	$\begin{bmatrix} .009 & . \\ 0 & .001 \end{bmatrix}$	$\begin{bmatrix} .008 & . \\ 0 & 0 \end{bmatrix}$
$a_s=.6$; $b_s=.4$	$\begin{bmatrix} .093 & . \\ .001 & .017 \end{bmatrix}$	$\begin{bmatrix} .098 & . \\ .002 & .018 \end{bmatrix}$	$\begin{bmatrix} .044 & . \\ 0 & .008 \end{bmatrix}$	$\begin{bmatrix} .050 & . \\ 0 & .009 \end{bmatrix}$	$\begin{bmatrix} .024 & . \\ 0 & .004 \end{bmatrix}$	$\begin{bmatrix} .024 & . \\ 0 & .004 \end{bmatrix}$	$\begin{bmatrix} .009 & 0 \\ 0 & .001 \end{bmatrix}$	$\begin{bmatrix} .008 & 0 \\ 0 & .002 \end{bmatrix}$

Table 13. Variances of the total indirect effect with moderate residual variance when the predictor (*X*) is continuous

Parameter	Sample size *n=50*;		Sample size *n=100*;		Sample size *n=200*;		Sample size *n=500*;	
	Average Variance	Sample Variance	Average Variance	Sample Variance	Average Variance	Sample Variance	Average Variance	Sample Variance
$a_s=.3$; $b_s=0$	$\begin{bmatrix} .027 & . \\ 0 & .004 \end{bmatrix}$	$\begin{bmatrix} .027 & . \\ 0 & .004 \end{bmatrix}$	$\begin{bmatrix} .012 & . \\ 0 & .002 \end{bmatrix}$	$\begin{bmatrix} .011 & . \\ 0 & .002 \end{bmatrix}$	$\begin{bmatrix} .006 & . \\ 0 & .001 \end{bmatrix}$	$\begin{bmatrix} .006 & . \\ 0 & .001 \end{bmatrix}$	$\begin{bmatrix} .002 & . \\ 0 & 0 \end{bmatrix}$	$\begin{bmatrix} .002 & . \\ 0 & 0 \end{bmatrix}$
$a_s=.6$; $b_s=0$	$\begin{bmatrix} .097 & . \\ 0 & .016 \end{bmatrix}$	$\begin{bmatrix} .108 & . \\ 0 & .017 \end{bmatrix}$	$\begin{bmatrix} .044 & . \\ 0 & .007 \end{bmatrix}$	$\begin{bmatrix} .044 & . \\ 0 & .007 \end{bmatrix}$	$\begin{bmatrix} .022 & . \\ 0 & .004 \end{bmatrix}$	$\begin{bmatrix} .022 & . \\ 0 & .004 \end{bmatrix}$	$\begin{bmatrix} .009 & . \\ 0 & .001 \end{bmatrix}$	$\begin{bmatrix} .008 & . \\ 0 & .001 \end{bmatrix}$
$a_s=.3$; $b_s=.1$	$\begin{bmatrix} .029 & . \\ 0 & .005 \end{bmatrix}$	$\begin{bmatrix} .030 & . \\ 0 & .005 \end{bmatrix}$	$\begin{bmatrix} .012 & . \\ 0 & .002 \end{bmatrix}$	$\begin{bmatrix} .013 & . \\ 0 & .003 \end{bmatrix}$	$\begin{bmatrix} .006 & . \\ 0 & .001 \end{bmatrix}$	$\begin{bmatrix} .006 & . \\ 0 & .001 \end{bmatrix}$	$\begin{bmatrix} .002 & . \\ 0 & 0 \end{bmatrix}$	$\begin{bmatrix} .002 & . \\ 0 & 0 \end{bmatrix}$
$a_s=.3$; $b_s=.4$	$\begin{bmatrix} .032 & . \\ .002 & .007 \end{bmatrix}$	$\begin{bmatrix} .039 & . \\ .003 & .008 \end{bmatrix}$	$\begin{bmatrix} .013 & . \\ .001 & .003 \end{bmatrix}$	$\begin{bmatrix} .013 & . \\ .001 & .003 \end{bmatrix}$	$\begin{bmatrix} .006 & . \\ .001 & .001 \end{bmatrix}$	$\begin{bmatrix} .006 & . \\ .001 & .001 \end{bmatrix}$	$\begin{bmatrix} .002 & . \\ 0 & .001 \end{bmatrix}$	$\begin{bmatrix} .002 & . \\ 0 & .001 \end{bmatrix}$
$a_s=.6$; $b_s=.1$	$\begin{bmatrix} .094 & . \\ 0 & .015 \end{bmatrix}$	$\begin{bmatrix} .114 & . \\ .001 & .016 \end{bmatrix}$	$\begin{bmatrix} .045 & . \\ 0 & .007 \end{bmatrix}$	$\begin{bmatrix} .048 & . \\ 0 & .007 \end{bmatrix}$	$\begin{bmatrix} .022 & . \\ 0 & .004 \end{bmatrix}$	$\begin{bmatrix} .022 & . \\ 0 & .004 \end{bmatrix}$	$\begin{bmatrix} .009 & . \\ 0 & .001 \end{bmatrix}$	$\begin{bmatrix} .008 & . \\ 0 & .001 \end{bmatrix}$
$a_s=.6$; $b_s=.4$	$\begin{bmatrix} .109 & . \\ .003 & .020 \end{bmatrix}$	$\begin{bmatrix} .119 & . \\ .003 & .021 \end{bmatrix}$	$\begin{bmatrix} .046 & . \\ .001 & .009 \end{bmatrix}$	$\begin{bmatrix} .047 & . \\ .001 & .009 \end{bmatrix}$	$\begin{bmatrix} .023 & . \\ .001 & .004 \end{bmatrix}$	$\begin{bmatrix} .023 & . \\ 0 & .005 \end{bmatrix}$	$\begin{bmatrix} .009 & . \\ 0 & .002 \end{bmatrix}$	$\begin{bmatrix} .009 & . \\ 0 & .002 \end{bmatrix}$

Table 14. Variances of the total indirect effect with high residual variance when the predictor (*X*) is continuous

Parameter	Sample size *n=50*;		Sample size *n=100*;		Sample size *n=200*;		Sample size *n=500*;	
	Average Variance	Sample Variance	Average Variance	Sample Variance	Average Variance	Sample Variance	Average Variance	Sample Variance
$a_s=.3$; $b_s=0$	$\begin{bmatrix} .051 & . \\ 0 & .008 \end{bmatrix}$	$\begin{bmatrix} .045 & . \\ 0 & .006 \end{bmatrix}$	$\begin{bmatrix} .016 & . \\ 0 & .003 \end{bmatrix}$	$\begin{bmatrix} .013 & . \\ 0 & .003 \end{bmatrix}$	$\begin{bmatrix} .007 & . \\ 0 & .001 \end{bmatrix}$	$\begin{bmatrix} .007 & . \\ 0 & .001 \end{bmatrix}$	$\begin{bmatrix} .002 & . \\ 0 & 0 \end{bmatrix}$	$\begin{bmatrix} .002 & . \\ 0 & 0 \end{bmatrix}$
$a_s=.6$; $b_s=0$	$\begin{bmatrix} .113 & . \\ -.001 & .018 \end{bmatrix}$	$\begin{bmatrix} .136 & . \\ -.001 & .020 \end{bmatrix}$	$\begin{bmatrix} .048 & . \\ 0 & .008 \end{bmatrix}$	$\begin{bmatrix} .044 & . \\ 0 & .008 \end{bmatrix}$	$\begin{bmatrix} .023 & . \\ 0 & .004 \end{bmatrix}$	$\begin{bmatrix} .024 & . \\ 0 & .004 \end{bmatrix}$	$\begin{bmatrix} .009 & . \\ 0 & .001 \end{bmatrix}$	$\begin{bmatrix} .008 & . \\ 0 & .001 \end{bmatrix}$
$a_s=.3$; $b_s=.1$	$\begin{bmatrix} .119 & . \\ .015 & .029 \end{bmatrix}$	$\begin{bmatrix} .061 & . \\ .015 & .014 \end{bmatrix}$	$\begin{bmatrix} .016 & . \\ 0 & .003 \end{bmatrix}$	$\begin{bmatrix} .014 & . \\ 0 & .002 \end{bmatrix}$	$\begin{bmatrix} .007 & . \\ 0 & .001 \end{bmatrix}$	$\begin{bmatrix} .007 & . \\ 0 & .001 \end{bmatrix}$	$\begin{bmatrix} .002 & . \\ 0 & 0 \end{bmatrix}$	$\begin{bmatrix} .002 & . \\ 0 & 0 \end{bmatrix}$
$a_s=.3$; $b_s=.4$	$\begin{bmatrix} .050 & . \\ .010 & .017 \end{bmatrix}$	$\begin{bmatrix} .044 & . \\ .010 & .015 \end{bmatrix}$	$\begin{bmatrix} .020 & . \\ .004 & .007 \end{bmatrix}$	$\begin{bmatrix} .018 & . \\ .005 & .007 \end{bmatrix}$	$\begin{bmatrix} .009 & . \\ .002 & .003 \end{bmatrix}$	$\begin{bmatrix} .009 & . \\ .002 & .003 \end{bmatrix}$	$\begin{bmatrix} .003 & . \\ .001 & .001 \end{bmatrix}$	$\begin{bmatrix} .003 & . \\ .001 & .001 \end{bmatrix}$
$a_s=.6$; $b_s=.1$	$\begin{bmatrix} .119 & . \\ -.001 & .020 \end{bmatrix}$	$\begin{bmatrix} .127 & . \\ -.002 & .021 \end{bmatrix}$	$\begin{bmatrix} .047 & 0 \\ 0 & .008 \end{bmatrix}$	$\begin{bmatrix} .045 & 0 \\ 0 & .009 \end{bmatrix}$	$\begin{bmatrix} .023 & . \\ 0 & .004 \end{bmatrix}$	$\begin{bmatrix} .021 & . \\ 0 & .004 \end{bmatrix}$	$\begin{bmatrix} .009 & . \\ 0 & .001 \end{bmatrix}$	$\begin{bmatrix} .009 & . \\ 0 & .002 \end{bmatrix}$
$a_s=.6$; $b_s=.4$	$\begin{bmatrix} .120 & . \\ .010 & .028 \end{bmatrix}$	$\begin{bmatrix} .120 & . \\ .010 & .029 \end{bmatrix}$	$\begin{bmatrix} .054 & . \\ .005 & .013 \end{bmatrix}$	$\begin{bmatrix} .061 & . \\ .004 & .014 \end{bmatrix}$	$\begin{bmatrix} .025 & . \\ .002 & .006 \end{bmatrix}$	$\begin{bmatrix} .027 & . \\ .003 & .006 \end{bmatrix}$	$\begin{bmatrix} .010 & . \\ .001 & .002 \end{bmatrix}$	$\begin{bmatrix} .011 & . \\ .001 & .002 \end{bmatrix}$

Table 15. Simulated rejection rates (% of replications) with a binary predictor (*X*)

Parameter	Sample size (n)			
	50	100	200	500
Residual variance: small				
a_s =.3; b_s =0	5.2	5.4	4.4	4
a_s =.6; b_s=0	10.2	5.2	5	5.4
a_s =.3; b_s=.1	16.6	28.8	49.6	88.8
a_s =.3; b_s=.4	92.4	100	100	100
a_s =.6; b_s=.1	19.8	30.6	50.2	87.6
a_s =.6; b_s=.4	96.8	100	100	100
Residual variance: moderate				
a_s =.3; b_s =0	0.4	1.6	2	4.2
a_s =.6; b_s=0	5	5.6	3.8	5.2
a_s =.3; b_s=.1	1.6	9	31	87.2
a_s =.3; b_s=.4	29.4	80.8	98.8	100
a_s =.6; b_s=.1	12.2	23.6	46.8	86.4
a_s =.6; b_s=.4	90.8	100	100	100
Residual variance: high				
a_s =.3; b_s =0	0.2	0	0.4	1.4
a_s =.6; b_s=0	1	1.8	1.4	2.2
a_s =.3; b_s=.1	0	1.4	6.2	56
a_s =.3; b_s=.4	5.2	17.6	51.2	93.8
a_s =.6; b_s=.1	3.2	8.2	28.6	85.2
a_s =.6; b_s=.4	33.2	80.6	100	100

Table 16. Simulated rejection rates (% of replications) with a continuous predictor (*X*)

Parameter	Sample size (n)			
	50	100	200	500
Residual variance: small				
a_s =.3; b_s =0	9.6	9.4	7.4	5
a_s =.6; b_s=0	9.2	7.2	6.4	4.8
a_s =.3; b_s=.1	20.6	30.8	48.2	88.6
a_s =.3; b_s=.4	95.8	100	100	100
a_s =.6; b_s=.1	24.2	27.2	50.8	89
a_s =.6; b_s=.4	96	100	100	100
Residual variance: moderate				
a_s =.3; b_s =0	4	5.4	5	3.6
a_s =.6; b_s=0	10.6	6.6	5.8	5.2
a_s =.3; b_s=.1	11.6	24.8	46	88
a_s =.3; b_s=.4	87.6	99.8	100	100
a_s =.6; b_s=.1	23.6	26.4	50.4	86.2
a_s =.6; b_s=.4	94.6	100	100	100
Residual variance: high				
a_s =.3; b_s =0	0.2	2	4.8	4.2
a_s =.6; b_s=0	5	4.8	4.6	3.6
a_s =.3; b_s=.1	1.4	7.6	33	83.6
a_s =.3; b_s=.4	27.8	77.8	98.4	100
a_s =.6; b_s=.1	12.8	27.2	44.2	87.8
a_s =.6; b_s=.4	87	99.8	100	100

2.2.4 Illustrative Example: University of Pittsburgh Physical Activity Study (PittPAS)

Data from PittPAS were used to illustrate the longitudinal mediational model described in the previous section. Details of the study was provided in the Arron's paper (Aaron DJ, Kriska AM et al. 1993). This longitudinal study was conducted to examine changes in physical activities of adolescents and recruited students from a single suburban school district. The study began in 1990 and included two phases: Phase I conducted from 1990 to 1993 and Phase II conducted from 2000 – 2003. In phase I, the interviews from 1990 to 1993 were denoted as the first, second, third and fourth interviews. In phase II, the individuals received their fifth interview during the period May 1999 through February 2003, denoted as R1 (median date, January 2001), and their sixth visit between June 2001 and September 2004, denoted as R2 (median date, March 2003). The questionnaires were adopted from a previous study (Kriska, Knowler et al. 1990) . Subjects were asked to indicate the type, the time spent and the intensity of typical sport and physical activities. Age was treated as an observation variable as time in this study, which was calculated as years between the interview date and date of birth. Students with different ages were recruited at the start of the study. Furthermore, due to the difficulty in tracking the individuals, the last two interview periods were overlapped, resulting in non-regular observation time. Random coefficient models are needed with the advantage to handle irregular structure presented in the current data set.

The study examined the baseline and trend in activity level in adolescence and young adulthood, as well as the differences between genders. Total hours per week spent in the activities in young adulthood (R1 and R2) was defined as the outcome, and total hours per week spent in the activities in adolescence (1990-1993) was used as the mediator and gender was defined as the predictor. A longitudinal mediational model was used to investigate if the activity experience in young adulthood could be caused by the experience in adolescence, and whether there is a differential effect of genders. The physical activity process consisted of two components: the initial status and the change with age. The data analysis was done using the SAS (Version 9.13) programming language.

Description of the Data

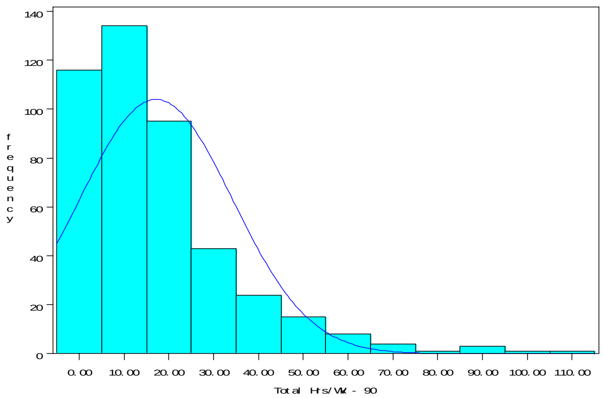
A total of 1245 individuals were recruited at the start of the study, of which 860 subjects had at least one observation in Phase I and at least one observation in Phase II were included in this analysis. Four hundred and nine (47.6%) were males and 451 (52.4%) were females.

Table 17. Demographic status of the total population through years

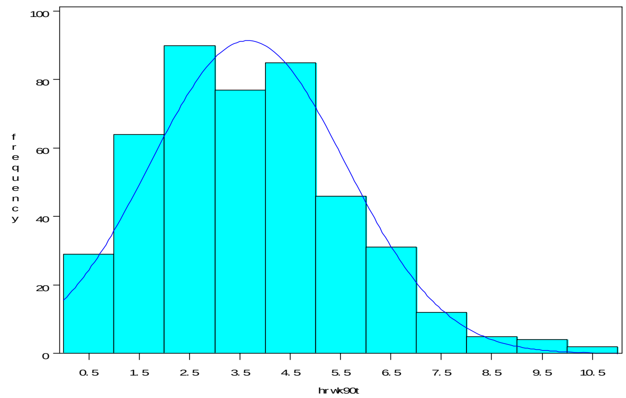
		Adolescence (Mediator)				Young Adulthood (Outcome)	
		1st	2nd	3rd	4th	5th	6th
Visit time (Year)		1990	1991	1992	1993	R1	R2
Age (Mean and S.d)		13.6(1.1)	14.6(1.1)	15.6(1.1)	16.6(1.1)	24.9(1.2)	26.9(1.2)
Subjects participated (N)		1171	1088	957	809	828	678
% of whole population		94.1	87.4	76.9	65.0	66.5	54.5
SEX:	Male (%)	51.6	52.6	52.5	52.4	47.6	45.8
	Female (%)	48.4	47.4	47.5	47.6	52.4	54.3

The square root transformation was applied to bring the distribution close to normal distribution (Figure 4). Panel 1 presented the outcome data (original and transformed) and Panel 2 presented the mediator data (original and transformed).

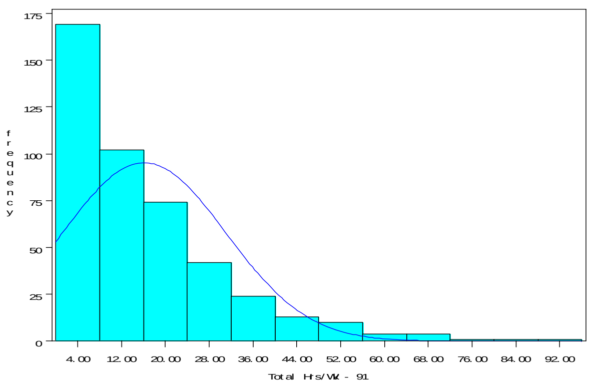
Panel 1 : Mediator Data



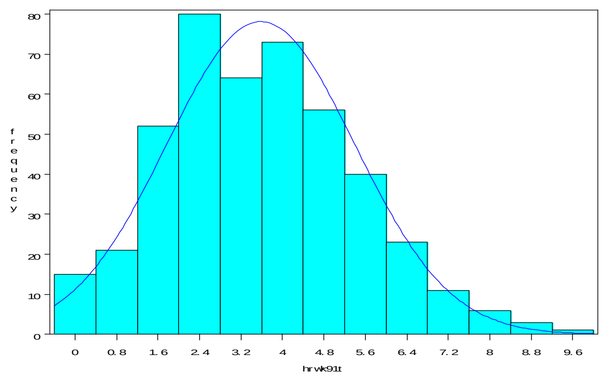
a) Original data: 1990



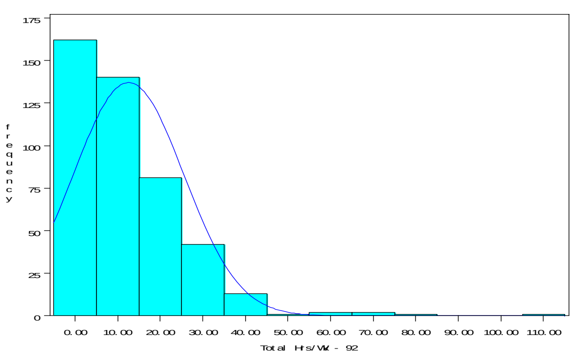
b) Transformed data: 1990



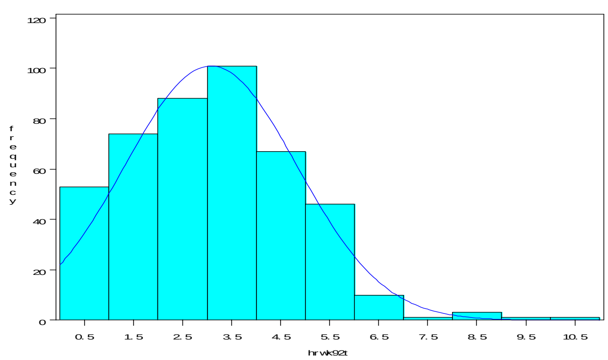
c) Original data: 1991



d) Transformed data: 1991

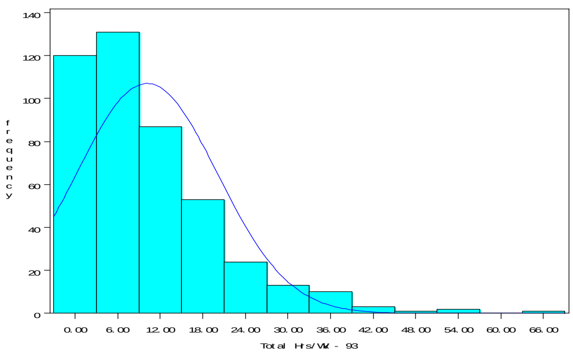


e) Original data: 1992

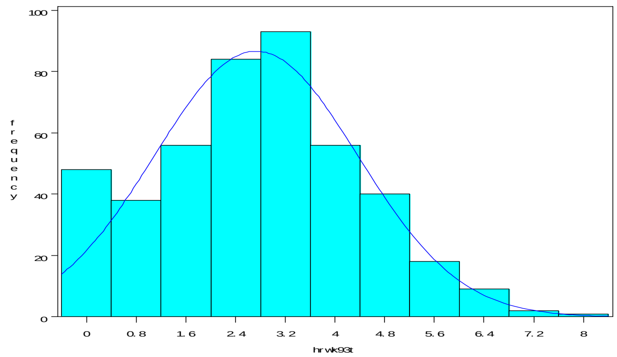


f) Transformed data: 1992

Figure 4 continued below

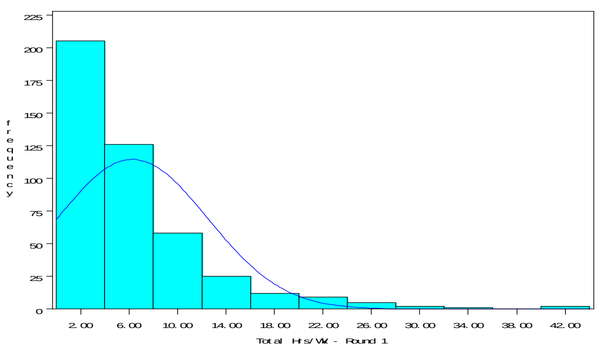


g) Original data: 1993

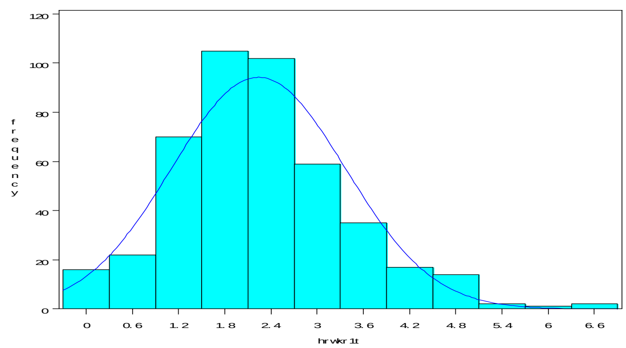


h) Transformed data: 1993

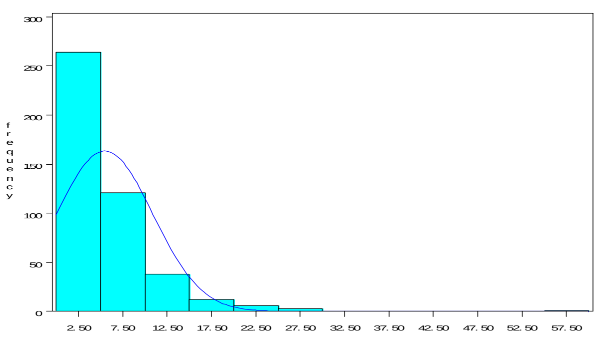
Panel 2 : Outcome Data



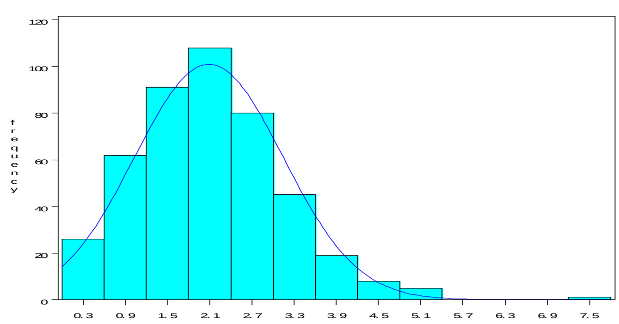
i) Original data: R1



j) Transformed data: R1



k) Original data: R2



l) Transformed data: R2

Fig 4. The distribution of the physical activities data (original and transformed)

The mean and standard deviations of physical activities time in adolescence and young adulthood were shown in Table 18 and Table 19. Overall, the physical activities time declined with age. As shown in Figure 5 and 6, in adolescence and young adulthood, the males spent more time in physical activities than females (Mean hours per week in 1990: $M_{\text{male}} = 23.9$; $M_{\text{female}} = 10.8$; Mean hours per week in 2001: $M_{\text{male}} = 8.1$; $M_{\text{female}} = 4.6$). The differences between males and females in slopes were not obvious.

Table 18. Means (standard deviations) of the mediator and the outcome

		Adolescence (Mediator)				Young Adulthood (Outcome)	
		1st	2nd	3rd	4th	R1	R2
Visit time		1990	1991	1992	1993	2001	2003
Physical Activities Time		17.1(17.1)	16.1(14.9)	12.6 (13.0)	10.1 (10.0)	6.3 (6.2)	5.5 (5.3)
Physical Activities:	Male	23.9(18.0)	22.1 (16.4)	17.3 (13.1)	14.3 (10.6)	8.1 (7.0)	6.7 (5.7)
	Female	10.8(13.4)	10.6 (10.7)	8.1 (11.1)	6.3 (7.5)	4.6 (4.8)	4.3 (4.9)

Table 19. Transformed means (standard deviations) of the mediator and the outcome

		Adolescence (Mediator)				Young Adulthood (Outcome)	
		1st	2nd	3rd	4th	R1	R2
Visit time		1990	1991	1992	1993	2001	2003
Physical Activities Time		3.7 (1.9)	3.6 (1.8)	3.1 (1.8)	2.7 (1.6)	2.2 (1.1)	2.1 (1.1)
Physical Activities:	Male	4.5 (1.8)	4.4 (1.7)	3.8 (1.6)	3.5 (1.5)	2.6 (1.2)	2.3 (1.1)
	Female	2.8 (1.7)	2.8 (1.6)	2.4 (1.6)	2.0 (1.5)	1.9 (1.0)	1.8 (4.8)

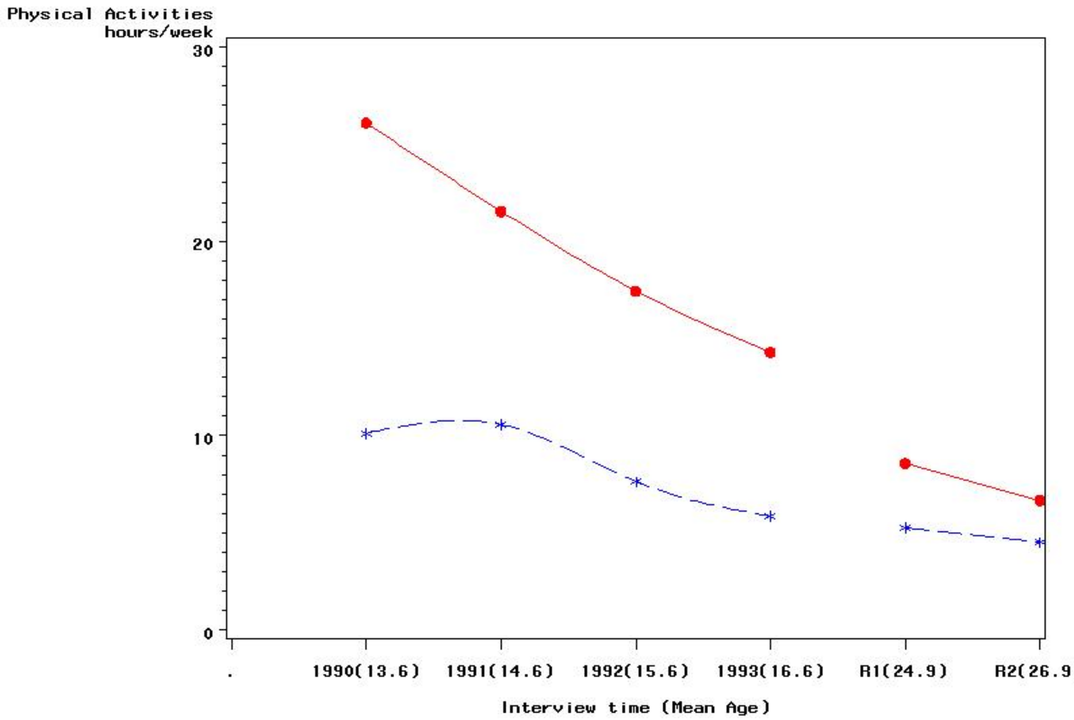


Fig 5. Physical activities through ages - original data

(dot-males; star- females)

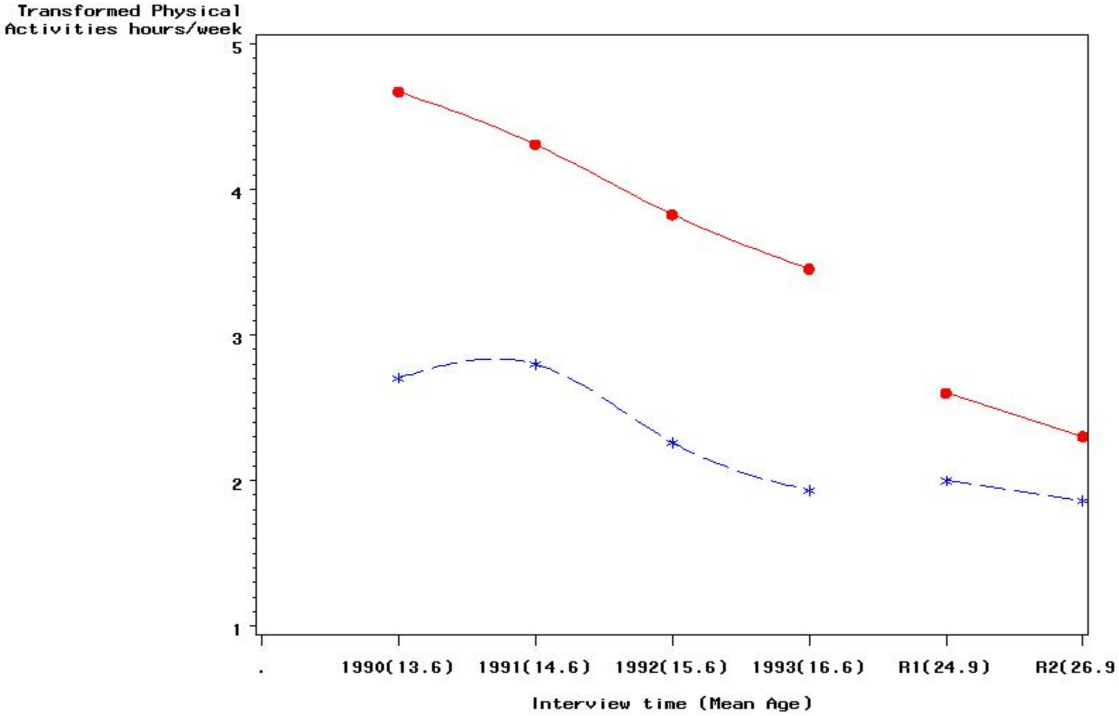


Fig 6. Physical activities through ages - transformed data

A Longitudinal Mediational Model for PittPAS

In the preliminary review and graphical display of the data, similar pattern was found both in adolescence and young adulthood. It was seen that the males exercised more but the differences in slopes were not obvious.

The longitudinal mediational model was used to explore if the differential effect of gender on young adulthood could be mediated by the previous physical activities experience in adolescence. Corresponding to equations 2.10, 2.11, and 2.15, the model consisted of three random coefficient models, denoted as Model 1, Model 2, and Model 3. The predictor variable was the gender (males=-0.5, females=0.5). The mediator was transformed physical activities time (total hours per week) in adolescence. The outcome was transformed physical activities time (total hours per week) in young adulthood. Age was treated as an observational "time" variable measured at the six time points.

$$Y_{ij} = \pi_0^y + \pi_1^y t_{ij}^y + \beta_{11} X_i + \beta_{12} X_i t_{ij}^y + D_0^y + D_1^y t_{ij}^y + \varepsilon_{ij} \qquad \text{Model 1}$$

$$Z_{ij} = \pi_0^z + \pi_1^z t_{ij}^z + a_1 X_i + a_2 X_i t_{ij}^z + D_0^z + D_1^z t_{ij}^z + \xi_{ij} \qquad \text{Model 2}$$

$$\begin{aligned} Y_{ij} = {} & \delta_0 + \delta_1 t_{ij}^y + \delta_2 X_i + \delta_3 X_i t_{ij}^y + b_1 \hat{D}_{0i}^z + b_3 \hat{D}_{1i}^z + b_2 \hat{D}_{0i}^z t_{ij}^y \\ & + b_4 \hat{D}_{1i}^z t_{ij}^y + D_{0i}^{y-z} + D_{1i}^{y-z} t_{ij}^y + \upsilon_{ij} \end{aligned} \qquad \text{Model 3}$$

In these equations, *i*=1,2,….,860; *j*=1, 2 in models 1 and 3; and *j*=1, 2, 3, 4 in model 2. The results of estimated parameters were shown in Table 20 and Figure 7.

Model 1 and Model 2 were fit to examine the difference of the initial status and the longitudinal change between males and females in physical activity time in adolescence and young adulthood, which were visualized in Figure 5. The initial status was shown as the intercept. The longitudinal change was shown as the slope of age.

There was significant difference in the initial status both in adolescence and young adulthood between genders (Coefficient of gender in Model 1 ($\hat{\beta}_{11}$) was -1.93, p=0.04; and Coefficient of gender in Model 2 ($\hat{a}_1$) was -2.56, p<.0001). The difference between genders in slope were not significant during the two periods (Coefficient of interaction of gender and age in Model 1 ($\hat{\beta}_{12}$) was 0.05, P=0.17; and Coefficient of interaction of gender and age in Model 2 ($\hat{a}_2$) was 0.06, P=0.14). Model 3 examined the effect of gender with the physical activities in young adulthood accounting for their previous experience (initial status and growth rate in adolescence). Akaike's Information Criterion (AIC) was used to assess the goodness of model fitness. Model 3 with the smallest AIC was considered as the best model. The significance of Model 3 was tested by the likelihood ratio test. The -2 log likelihood difference between Model 1 and Model 3 was significant ($\chi^2(4)$ = 55.2, p<0.0001), and indicated that inclusion of the mediator in the model improved the model fit significantly.

Table 20. Estimated parameters in Model 1, 2, and 3

Model 1 (AIC=4558.8; -2 Log Likelihood = 4550.8)	
Fixed Effect Parameters	**Estimates**
Gender: β_{11}	-1.9307* (0.93)
Interaction of Age and Gender: β_{12}	0.05318 (0.04)
Model 2 (AIC= 10936.3; -2 Log Likelihood=10928.3)	
Fixed Effect Parameters	
Gender: a_1	-2.5630*** (0.63)
Interaction of Age and Gender: a_2	0.05678 (0.04)
Variance Parameters	
$\begin{bmatrix} \sigma_{a_1}^2 & \sigma_{a_1 a_2} \\ \sigma_{a_1 a_2} & \sigma_{a_2}^2 \end{bmatrix}$	$\begin{bmatrix} 0.3984 & -0.02586 \\ -0.02586 & 0.001715 \end{bmatrix}$
Model 3 (AIC= 4503.6; -2 Log Likelihood=4495.6)	
Fixed Effect Parameters	
Gender: $\beta_{21} + a_1 b_1 + a_2 b_3$	-2.1259* (0.92)
Interaction of Age and Gender: $\beta_{22} + a_1 b_2 + a_2 b_4$	0.06078 (0.04)
b_1	0.8856 (0.57)
b_3	4.9209 (14.4)
b_2	-0.02072 (0.02)
b_4	0.07354 (0.55)
Variance Parameters	
$\begin{bmatrix} \sigma_{b_1}^2 & \sigma_{b_1 b_2} & \sigma_{b_1 b_3} & \sigma_{b_1 b_4} \\ \sigma_{b_1 b_2} & \sigma_{b_2}^2 & \sigma_{b_2 b_3} & \sigma_{b_2 b_4} \\ \sigma_{b_1 b_3} & \hat{\sigma}_{b_2 b_3} & \sigma_{b_3}^2 & \sigma_{b_3 b_4} \\ \sigma_{b_1 b_4} & \sigma_{b_2 b_4} & \hat{\sigma}_{b_3 b_4} & \sigma_{b_4}^2 \end{bmatrix}$	$\begin{bmatrix} .3197 & . & . & . \\ -.01219 & .000468 & . & . \\ 7.0750 & -.2696 & 207.26 & . \\ -.2696 & .01034 & -7.9151 & .3041 \end{bmatrix}$

p<0.5 ***p<0.0001

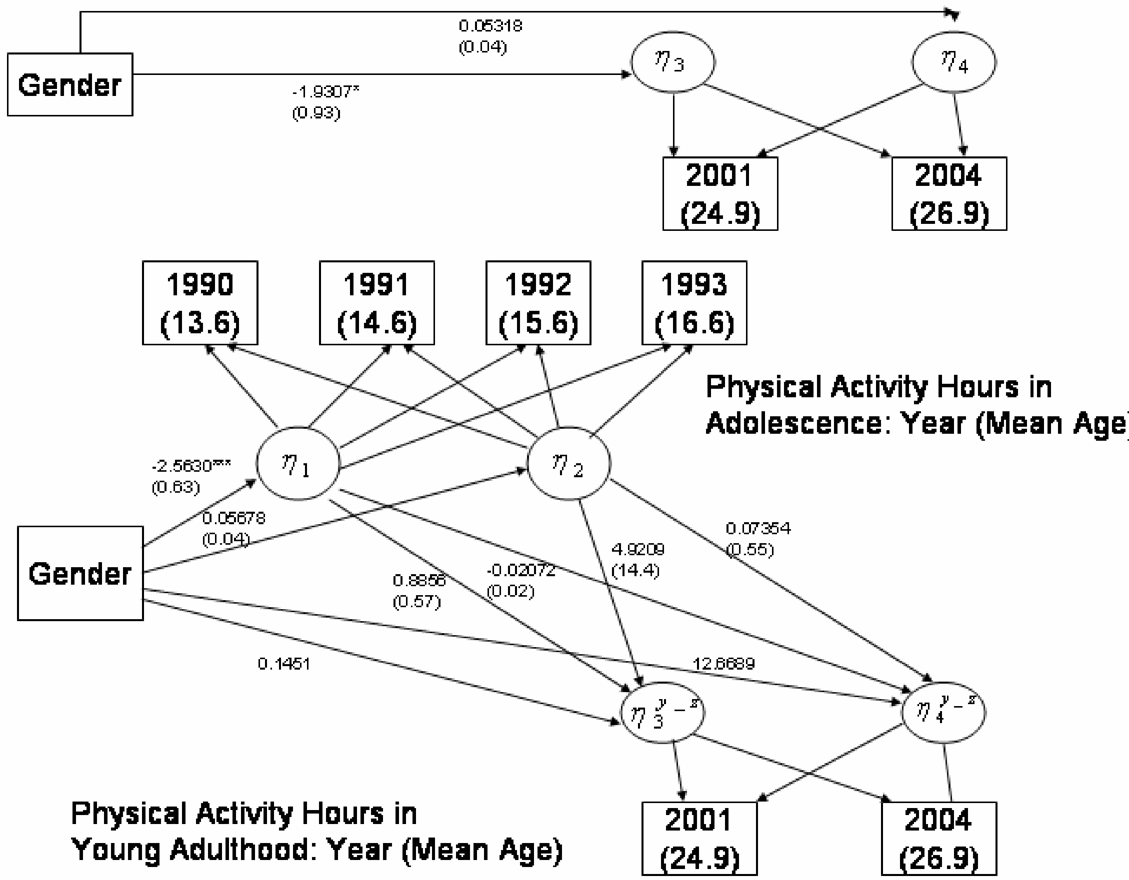


Fig 7. A longitudinal model to investigate the indirect effect for PittPAS

Gender= predictor; Physical Activities in Young Adulthood = outcome;
Physical Activities in adolescence = Mediator;

η_1 = initial status of mediator; η_2 = growth rate of mediator;

η_3^y = initial status of outcome; η_4^y = growth rate of outcome;

η_3^{y-z} = initial status of outcome when accounting for η_1 and η_2 ;

η_4^{y-z} = growth rate of outcome when accounting for η_1 and η_2 ;

The estimated total direct effect in this longitudinal mediational model given by $\hat{\mathrm{f}}=(\hat{a}_1\hat{b}_1+\hat{a}_2\hat{b}_3,\quad \hat{a}_1\hat{b}_2+\hat{a}_2\hat{b}_4)$, equals to (-1.990381, 0.057273). Using the function in equation 2.18, the estimated variance-covariance of the total indirect effect is $\begin{bmatrix} 0.8375543 & -0.032861 \\ -0.032861 & 0.0013031 \end{bmatrix}$. The sample size in our study (*n*=860) is relatively large to satisfy the large sample size assumption which makes the two components in the vector $\hat{\mathrm{f}}$ approximately follow bivariate normal distribution. The result of the hypothesis test showed the total indirect existed ($\chi^2(2) = 36.100665$, p<0.0001). Let $\alpha = .05$, the bootstrap critical interval for the test statistic using BS-I is (0.066434, 7.872479). Therefore, we would reject the null hypothesis. This means that the differential effect of gender on physical activity in young adulthood is inferred to be mediated by the previous physical activities experience in adolescence.

In our mediational model, the initial status and the change over ages were considered as two components of the mediator (physical activities experience in adolescence) and the outcome (physical activities experience in young adulthood). Males reported higher level of physical activity in adolescence than females, as well as in young adulthood. Using the mediational model, we found the differential effect of gender on physical activity in young adulthood is inferred to be mediated by the previous physical activities experience in adolescence.

2.2.5 Public Health Issue for Mediational Analysis in PittPAS

The study of the behavior in physical activities is an important issue in psychosomatic research. Researchers have indicated that physical exercise could effectively reduce the morbidity and mortality from chronic diseases including cardiovascular disease and diabetes (Powell, Thompson et al. 1987).

Using the data from Amsterdam Growth and Healthy Longitudinal Study with 232 subjects measured during 15 years between age of 13 to 27, Mechelen and his colleagues found that males are more active than females and the amount of physical activity declines with increasing age (Mechelen, Twisk et al. 2000). However, there is little information on the causal relationship between the physical exercise profile in adolescence and that in young adulthood. This profile includes onset and the longitudinal change. To fully understand the development of physical activity patterns throughout the life span, this causal relationship needs to be examined. In the current thesis, we found that patterns of physical exercise in adolescence and young adulthood are similar. More importantly, using the mediational analysis, we found that the differential effect of gender on physical experience in young adulthood is inferred to be caused by the previous physical experience in adolescence. Therefore, an approach to improve the activities level in adulthood is increasing the physical activities level in adolescence, which could be more applicable and efficient by interferential and educational programs through organization of schools and community. The effect of increasing the physical activities level in adolescence will be consistently extended to the young adulthood. Also, increasing the physical activities in girls could reduce the distinction between the males and females in young adulthood.

2.2.6 Discussion

Multilevel models are now becoming common in different areas of the social and behavioral sciences. The random coefficient model is able to handle time-unstructured data, which is a common feature in many longitudinal studies. We have discussed one scenario where the outcome process and the mediational process are described by linear growth curves. The total indirect effect of the predictor is defined as the effect of the predictor on the initial status and the growth rate of the outcome after accounting for the mediating effect of the initial status and the growth rate of the mediator. Inferential methods for the total indirect effect are proposed, using a formulation by random coefficient models. Results from a simulation study indicate the reliability of the proposed methods with large samples. An example, analyzing PittPAS, illustrated the methods we propose.

The mediational model in this paper requires the assumption that the mediator is measured before the outcome and after the predictor. Without this assumption, it will be difficult to build a logical causation between the three variables. In the event of significant total indirect effect in the mediational model, post-hoc analysis using simple mediational models should follow.

The equations in the mediational model in this paper are under the usual assumptions of random coefficient models. Moreover, the parametric hypothesis test assumes the elements in the estimates of the total indirect effect follow a bivariate normal distribution which requires large sample size. The proposed bootstrap test could release this assumption. The performance of these methods should be examined under more general condition using Monte Carlo studies. Further work could focus on assessing the performance of these methods under such circumstances.

3.0 CONCLUSION

The main purpose of the first part of the dissertation was to describe the multivariate mediational model with one mediator in a cross-sectional mediational study and derive the corresponding inferential test procedures for the indirect effect. Two parametric methods that are extensions of the Clogg test (ECLG-P) and the Sobel test (ESOB-P), and two bootstrap methods were proposed. Using simulations, Type I error rates and power rates were compared. It was concluded that, in the presence of the correlation between the predictor and the mediator, ECLG-P provided the maximum power and the most accurate Type I error rate. As the correlation between the predictor and mediator is one of the key requirements for a variable to be a mediator we recommend that researchers should examine this correlation before doing any mediational analysis. The performance of the bootstrap methods as measured by power values was less satisfactory than the ECLG-P method.

In the second part of the dissertation, we have described a longitudinal mediational model where the outcome process and the mediational process were described by linear growth curves. The total indirect effect of the predictor was defined as the effect of the predictor on the initial status and the growth rate of the outcome after accounting for the mediating effect of the initial status and the growth rate of the mediator. Inferential methods for the total indirect effect used a formulation by random coefficient models to accommodate time unstructured data. Results from a simulation study indicated the reliability of the proposed methods with large samples. An illustrative example using data from PittPAS was given. It was concluded that random effects models provide a useful tool in longitudinal mediational modeling endeavor.

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